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SPECIAL LISTING

CURRENT CANCER RESEARCH

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CLINICAL DIAGNOSTIC RADIOLOGY AND RADIATION THERAPY

AUGUST 1981

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB)

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Dear Cancer Researcher:

This **SPECIAL LISTING** of Current Cancer Research Projects is a publication of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) Program of the National Cancer Institute. Each **LISTING** contains descriptions of ongoing projects in one selected cancer research area. Approximately 55 areas are covered in separate **SPECIAL LISTINGS.** Each title of these **SPECIAL LISTINGS** is published annually.

The purpose of these **LISTINGS** is to promote and facilitate the exchange of information among cancer scientists. The project descriptions in the **LISTINGS** are provided by cancer scientists from more than 80 different countries.

Descriptions of more than 20,000 other current cancer-related projects are on the CANCERPROJ data base. This cancer data base is available as part of the MEDLINE System of the National Library of Medicine and can be searched by librarians at some 1400 locations in the U.S. and in 12 other countries. CANCERPROJ is also available via the new EURONET data base system in EUROPE.

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CURRENT CANCER RESEARCH

I. RADIOLOGIC METHODS IN CANCER DIAGNOSIS

A. X-RADIOGRAPHY

1. COMPUTERIZED TRANSAXIAL TOMOGRAPHY

1. METHODOLOGY USING CONTRAST AGENTS TO IMPROVE DETECTION OF SMALL LIVER METASTASES WITH COMPUTERIZED X-RAY TOMOGRAPHY

Seltzer, S. E., Davis, M. A., Adams, D. F., Harvard University, Boston Campus, School of Medicine, Dept. of Radiology, *25 Shattuck St. Boston, Massachusetts,* 02115, United States of America

OBJECTIVES: To develop and test new contrast agents capable of improving the detectability of small liver lesions. To identify reliability by computed tomography (CT) lesions smaller than 1 cm in size. Such an accomplishment would improve the diagnosis, staging, and treatment of large numbers of patients, especially those with cancer.

APPROACH: (1) Synthesis of New Contrast Agents - Materials incorporating elements of high atomic number will be synthesized. Materials of atomic numbers 50 to 66 are the best absorbers of X-rays from the 120 kVp CT beam. The approach to the design of such agents is based on viewing the liver-lesion system as composed of six major compartments: a) intravascular; b) extracellular, extravascular; c) reticuloendothelial (RE) (Kupffer) cells; d) polygonal cells; e) bile ducts; f) the lesion itself. Standard, iodinated agents have easy access to compartments a) and b) in both normal livers and tumors. We will synthesize and test several materials that will selectively be taken up into each of compartments c) through f).

This proposal emphasizes development of particulate agents that are incorporated into RE cells. Cerium, dysprosium, and gadolinium oxide suspensions (particle size averaging less than 2 microns) have been synthesized. Iodinated starch particles and iodine-containing liposomes are being perfected.

(2) Effectiveness Evaluation in Animal Models - The biodistribution, liver/tumor ratios, and clearance of each new agent will be evaluated in animal liver tumor models (rabbit V2 carcinoma, rat Walker 256 carcinosarcoma). Computed tomograms of the livers of animals with experimental lesions will be obtained using the new and the standard contrast agents. Rare earth oxides, taken up selectively by RE cells, provide greater and longer liver opacification than standard agents. In addition, the acute, subacute, and chronic toxicities of promising agents will be evaluated.

2. DETECTION OF LIVER METASTASES WITH X-RAY TOMOGRAPHY

Adams, D. F., Peter Bent Brigham Hospital, *721 Huntington Ave., Boston, Massachusetts,* 02115, United States of America

The objective is to improve x-ray detection of early metastatic lesions in the liver. Specifically, methodology will be developed to enhance computerized x-ray tomographic imaging of liver tissue by means of specific contrast media so that small (1 cm or less) liver metastases can be visualized. Independently and not as an agent of the Government, the Contractor will develop and clinically test the necessary methodology for improved detection of early (small) liver metastases with computerized x-ray tomography using contrast media.

3. VALUE OF COMPUTERIZED WHOLE-BODY TOMOGRAPHY COMPARED WITH OTHER ROENTGENODIAGNOSTIC METHODS, ULTRASOUND, AND NUCLEAR MEDICINE

Boijsen, E., Lunderquist, A., Tylen, U., Mortensson, W., Ekelund, L., Landberg, T., Lamm, I., University Hospital of Lund, Dept. of Diagnostic Radiology, *E. Blocket, S22185 Lund, Sweden*

The diagnostic results of a third generation CT-scanner with 4.2 seconds of exposure (Philips Tomoscan 300) will be evaluated in relation to other diagnostic modalities. The following subjects are particularly studied:

A) Correlation between ultrasonography, CT, PTC, and angiography in patients with jaundice caused by malignant lesions. The most suitable diagnostic procedure is to be defined.

B) Value of CT in order to define hepatic trauma caused by PTC or PIP (percutaneous transhepatic portography) where CT probably will provide better information than other methods in defining complications.

C) Diagnosis of primary and secondary liver tumors and follow-up after treatment with intraarterial cytostatics, dearterialization and/or liver resection. Diagnosis of primary and secondary liver metastases will be improved with CT combined with infusion of contrast medium into the hepatic artery. Effects of treatment can best be followed with CT combined with intraarterial injection. Different modalities of treatment can be better evaluated with CT.

D) Contrast media and their importance for maximum tumor enhancement in CT. Contrast media are infused in various concentrations and amounts in order to find the proper mode of introduction.

E) Bronchial carcinoma. Evaluation of operability and effects of intraarterial treatment with cytostatics.

F) CT in bladder carcinoma. The main purpose is to improve a clinical evaluation of local spread of bladder tumors.

G) CT in oncology. In order to improve more exact radiation treatment.

4. AN INTEGRATED SYSTEM FOR THE QUANTITATIVE ANALYSIS OF AXIAL TOMOGRAPHS OF PATIENTS WITH CEREBRAL EDEMA

Gooding, M. R., Danny, P. J., Cook, G. B., Morgan, C. H., Whitehead, D. G., Hull Royal Infirmary, Ward 9, *Anlaby Rd., Kingston upon Hull, Hull HU3 2JZ, England, United Kingdom*

OBJECTIVE: Development of computer-based system for quantitative analysis and display of EMI Scanner tomographs, incorporating computation of density statistics and volume of specified regions of interest. Angular reconstructions of the original data sets to facilitate tomographic views of any plane, and the application of this system to monitor the effects of various treatments (steroid therapy with/without tumor excision with/without irradiation) on cerebral edema.

APPROACH: 1) In cooperation with Hull University (Depts. of Computer Studies and Electronic Engineering), development of image display system similar to that on the EMI Scanner. 2) Writing of software package comprising a set of programs enabling the user to retrieve/modify/store scan data, display and annotate individual scans and further analyze data - picture subtraction, area/volume analysis, density profiles, angular reconstuctions. 3) Collation of clinical data (from Hull, R.I., Atkinson Morley's Hospital, Royal Marsden Hospital) on approximately 100 patients suffering from malignant brain tumors and 60 patients with cerebral edema.

PROGRESS: 1) Image display system completed - slave monitor and camera to be added. 2) All 2-dimensional scan

analysis implemented -analysis of volumes under development. 3) Approximately 20 percent of clinical data acquired.

5. TOPOGRAPHY OF BRAIN TUMORS - COMPUTERIZED TRANSFER OF COORDINATES FROM RADIOLOGIC PROCEDURES (ABBREV)

Greitz, T., Karolinska Sjukhuset, Dept. of Neuroradiology, *S10401 Stockholm, Sweden*

This project aims at the development of a patient head fixation device combined with modalities for exact delineation of the location and spread of brain tumors in order to improve their radiological and surgical treatment. This system will allow exact and automatic transfer of spatial information from a diagnostic situation (computer tomography, plain skull radiography, conventional tomography, angiography, pneumoencephalography, brain scintigraphy, positron emission tomography, etc.) to a therapeutic situation (biopsy, puncture of cystic lesions, radiosurgery, radiotherapy, etc.).

6. EMISSION COMPUTED TOMOGRAPHY OF LOCAL CEREBRAL FUNCTIONS

Kuhl, D. E., University of California, Los Angeles Campus, School of Medicine, Dept. of Radiological Sciences, *2025 Zonal Ave., Los Angeles, California*, 90024, United States of America

We propose to develop relatively atraumatic study methods that may be applied to patients for accurate determination of measurements of local cerebral function in terms of absolute values of circulation and metabolism. By means of emission computed tomography of appropriately chosen radioactive indicators administered intravenously, tracer distributions will be quantified with three-dimensional localization. Once validated, these methods will be applied to improve understanding of basic human cerebral physiology and will be evaluated for their usefulness in enhancing the diagnosis and management of patients with cerebrovascular disease, seizure disorders, and metabolic encephalopathies.

7. 3-D TOMOGRAM VIEWER FOR CANCER DETECTION AND THERAPY

Baxter, B. S., Reading, J., Anderson, R. E., Johnson, S. A., Nelson, J. A., Lee, T., Leavitt, D. D., Utah Higher Education System, University of Utah, School of Medicine, Dept. of Radiology, *1400 E. 2nd S., Salt Lake City, Utah*, 84112, United States of America

The objective of this project is to study the clinical applications of a new viewer for tomographic scans which allows the physician to examine multiple scan sections simultaneously in the proper relationship in all three dimensions. Test images shown on a prototype device clearly show stereopsis and parallax depth cues characteristic of a real three-dimensional object. We are evaluating this device using x-ray CT and B-scan ultrasound data, also radiation therapy dose profiles, to determine the extent to which these data are more comprehensible when viewed in 3-D. Our primary objective in this reporting period is to complete the construction and checkout of a viewing device suitable for evaluation in a clinical environment. A second objective added midway through the current period is to evaluate the use of the viewing as a means of guiding the stereotaxic surgical frame developed by Dr. R. A. Brown for invasive procedures in the brain. To accomplish this objective it will be necessary to attach the completed viewer to a small portable computer system so the unit may be moved to and from the neurosurgery operating suite.

8. CHEST CT-MEDIASTINOSCOPY STUDY

Adler, S. N., Rogers, R. M., Traub, S. P., Johnson, T., Eaton, B. G., Allen, E. W., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Pulmonary Disease Section, *921 N.E. 13th St., Oklahoma City, Oklahoma*, 73104, United States of America

PURPOSE: To study prospectively the sensitivity and specificity of plain chest x-ray, mediastinal tomography, gallium scan, and chest computed tomography (CT) and in the evaluation of proven primary carcinoma of the lung.

REASON FOR STUDY: 1. To ascertain if chest CT can reduce and/or eliminate the need for mediastinoscopy or second left interspace exploration in the staging of patients with otherwise resectable lung cancer. This would be desirable since: a) The morbidity of the procedure is 1.5-3% in large series with complications such as bleeding, infection, and even death (0.9%). b) The sensitivity of mediastinoscopy is 85-95%. c) The cost of mediastinoscopy is about $1000 plus a hospital day as opposed to chest CT which costs $292 without infusion of contrast. d) CT is non-invasive and repeatable. 2. To compare the efficacy of more conventional chest and mediastinal imaging technics with chest CT.

METHODS: All Oklahoma City VAMC patients with primary lung cancer in whom surgery is not contraindicated by virtue of age, pulmonary function, distant metastases histology, malignant effusion, or general medical or other disqualifying factors described in the literature, would undergo plain chest x-ray, mediastinal tomography, gallium scanning, and CT of the thorax before undergoing mediastinoscopy and possible thoracotomy. The plain chest x-ray and chest CT would be read by two separate radiologists, the mediastinal tomograms by one radiologist, and the gallium scan by one nuclear medicine specialist. All the readers would be blinded from each other's interpretation. The interpretations would be designed as 'positive' or 'negative' for mediastinal metastases. These results would then be correlated with tissue data obtained at surgical mediastinal and/or thorax exploration.

9. THE USE OF COMPUTED TOMOGRAPHIC SCANNING IN ONCOLOGY

Brenner, D. E., Aisner, J., Wiernik, P. H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Section of Medical Oncology, *Baltimore, Maryland*, 21201, United States of America

The advent of the computed tomographic scan has opened the possibility of locating, biopsing, and sequentially analyzing masses in previously inaccessible areas. To assess this technique, we have devised projects to prospectively study the capabilities and drawbacks of this technology. Fourteen patients with advanced carcinoma of the cervix have been evaluated preoperatively with good correlation for the presence of retroperitoneal adenopathy. Biopsies under CT guidance have provided adequate tissue in 75% of 25 patients studied. Ovarian carcinomas are being studied prospectively with 92% predictive accuracy. Other studies include serial assessments of other tumors, particularly lung tumors, and tumor volume studies. Further patient entries will provide more meaningful data in all projects described.

10. COMPUTED TOMOGRAPHY IN EVALUATION OF ENDOCRINE PANCREATIC TUMORS, PANCREATIC AND KIDNEY CARCINOMA (ABBREV)

Hemmingsson, A., University Hospital, Dept. of Diagnostic Radiology, *S75014 Uppsala 14, Sweden*

OBJECTIVE: Evaluation of CT, gray scale ultrasonography, scintigraphy and conventional roentgenologic methods will be made in diagnosis, follow-up and spread of endocrine pancreatic tumors, pancreatic carcinoma and kidney carcinoma. Image enhancement with frequency filtration in computed tomography will also be investigated.

APPROACH: Phantom and clinical examination of liver, pancreas and kidney tumors.

11. INVESTIGATION OF COMPUTERIZED AXIAL TOMOGRAPHY AS AN AID FOR RADIOTHERAPY IN CARCINOMA OF THE LUNG

Mira, J. G., Guinto, F. C., Fullerton, G. D., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Radiology Service, *San Antonio, Texas*, 78284, United States of America

PROGRESS REPORT UP TO DATE: A total of 11 patients have been placed on this project. Because we still have some remaining funds and because we expect to put more patients on this project in the future, a six-month extension has been requested and granted by the Subcommittee of the Institutional Review Board.

A preliminary report on the results of this project was done in September, 1979. It was based on these patients and a few others in which chest scans for carcinoma of the lung were done outside our project. This report was the result of a presentation at the American Society of Therapeutic Radiologists meeting in October, 1979. A summary of our results is as follows: (1) Atelectasis can be diagnosed only if characteristic

shapes are displayed. This was seen in 4 of 8 scans taken to clarify the etiology of diffuse lung infiltrations and confirmed by follow-up of 2 cases. CAT numbers for atelectasis are too close to tumor CAT numbers to help in differential diagnosis. (2) Tumor CAT numbers measured in 6 patients showed too much variability within the same tumor and in relation to other normal structures to be of help. (3) However, CAT numbers for effusions are consistently lower than those for tumor and atelectasis and, hence, of value in differential diagnosis. (4) Absolute CAT numbers might be meaningless, as numbers for the same structures vary widely from patient to patient. However, numbers compared within each patient are significant. (5) Contrast enhancement was of no help with the methods used. (6) CAT numbers might be useful to differentiate recurrent tumors from post-radiotherapy fibrotic shadows. (7) Large variations in lung CAT numbers have been found. This might be important in treatment planning calculations.

12. RECTAL CARCINOMA - IMAGING STUDY

Thompson, W. M., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Radiology Service, *508 Fulton St., Durham, North Carolina*, 27705, United States of America

OBJECTIVE: To evaluate the potential of computerized tomography and diagnostic ultrasound for the early detection of local recurrence of rectal carcinoma.

PLAN: Patients with proven rectal carcinoma will have a barium enema, ultrasound and computerized tomography of the pelvis just prior to surgical resection of the tumor. They will then be studied three weeks, six months, one year, eighteen months and two years following surgical resection by both computerized tomography and ultrasound. This study will last approximately four to five years. We anticipate ertering ten to fifteen patients per year into the study.

13. DEVELOPMENT OF RADIOTHERAPY TREATMENT PLANNING SYSTEM USING COMPUTED TOMOGRAPHY

MacDonald, J. S., Hodson, N. J., Hobday, P. A., Parker, R. P., Husband, J. E., Royal Marsden Hospital, Dept. of X-Ray, *Downs Rd., Sutton SM2 5PT, Surrey, England, United Kingdom*

OBJECTIVE: To develop a unified radiotherapy treatment planning system by linking a CT scanner (EMI 5005) and a radiotherapy treatment planning system (RAD 8).

APPROACH: Hitherto the basic weakness of dose planning systems has been inadequate knowledge of the accurate outline and internal anatomy of the patient and also the location, shape and size of the tumor. The amount of tissue traversed by the radiation beams has had to be estimated and relative densities assigned to tissues. By using CT cuts through the tumor, taken under the same conditions that exist during radiotherapy, an accurate outline can be obtained automatically and the tissue densities assessed by their EMI numbers. All the information from the CT scan is available to the planning computer.

PROGRESS: Work on the prototype has been completed.

14. RADIATION THERAPY TREATMENT PLANNING USING COMPUTERIZED TOMOGRAPHY INTERFACED WITH A TREATMENT PLANNING SYSTEM

Padikal, T. N., Syed, D., Fredrickson, H. A., Glatstein, E., Chang, M., Roberson, P. L., Fraass, B. A., Tepper, J., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Radiation Physics & Computer Automation Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

This project deals with a CT based treatment planning system for clinical use in radiation therapy. A large data base, generated from the teletherapy equipment (Mev. XII and Mev. VI), has been entered into the system and a faithful representation of the radiation field in digital form has been accomplished. External beam treatment planning has been well documented; brachytherapy documentation has been completed. Color-coded isodose distributions can be superimposed on selected CT cuts. This has improved the methods of dose delivery. The utilization of the system in routine treatment planning has dramatically increased.

15. DOSE REDUCTION X-RAY COMPUTED TOMOGRAPHY

Robb, R. A., Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota*, 55901, United States of America

OBJECTIVE: To improve detection of early and/or small cancer lesions by developing and demonstrating the clinical feasibility of appropriate algorithms for producing satisfactory computed x-ray tomography at significantly lower radiation dosages than those currently required.

16. EFFECTIVENESS OF COMPUTED TOMOGRAPHY

Moran, P. R., University of Wisconsin, Madison Campus, Center for the Health Sciences, *500 Lincoln Dr., Madison, Wisconsin*, 53706, United States of America

This is part of a broader project. A summary of this subproject is not available.

2. IMAGE ANALYSIS OF RADIOGRAPHS

17. IMAGING IN DETECTION OF EARLY PANCREATIC CANCER

Moossa, A. R., University of Chicago, Pritzker School of Medicine, Dept. of Surgery, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

OBJECTIVES: To establish methods for early detection of pancreatic cancer. To design and be capable of carrying out an extensive and definitive study to improve and evaluate imaging capabilities in the detection of early pancreatic cancer by having available advanced imaging equipment and capability in areas such as ultrasound, computerized axial tomography, etc.; having clinical facilities available to adequately test the efficacy of these modalities; carrying out adequate pathology review, in addition to which pathology slides, blocks, and pathological material will be made available for consultative review; and determining the number of patients to be entered into this study in order to allow for adequate statistical comparisons to be made.

18. COMPUTER-AIDED IMAGE RECOGNITION

Sklansky, J., Barnes, C. W., Sankar, P. V., Kawata, S., Milne, E. N., Nalcioglu, O., Roeck, W., Root, W. E., Kimme Smith, C., Cohen, A., University of California, Irvine Campus, School of Engineering, Dept. of Information & Computer Science, *Irvine, California*, 92664, United States of America

Our objectives are: a) to test our computer algorithms for helping radiologists detect lung tumors in chest radiographs and measure the extent of ductal prominence in mammograms in a realistic clinical setting, b) to increase the sensitivity and accuracy of detecting radiographic images of lung tumors and measuring the extent of ductal prominence in mammograms at the UCI Medical Center and c) continued improvements in our computer algorithms for detecting, locating, enhancing, and analyzing medically important objects in radiographic images.

Our research is organized into three units: 1) object detection and analysis, 2) image filtering, and 3) image-guided tomography.

We shall test the clinical effectiveness of our systems for computer-aided detection of lung tumors in chest radiographs and for measuring the extent of ductal prominence in mammograms. We also plan to increase the power and speed of our computer techniques for aiding the analysis of radiographs using: heap sorts in boundary following, medically orientated data structures in digitized radiographs, textural features based on Markov models, and piecewise linear classifiers.

We plan to exploit our techniques of block-approximated, zonal filtering for enhancement and deblurring of radiographs.

We plan to assimilate our techniques of boundary detection into coarse-fine computed tomography, in order to obtain adequate detail in selected regions of interest with reduced doses.

BIBLIOGRAPHIC REFERENCES: J. Sklansky, On the Hough Technique for Curve Detection, IEEE Transactions on Computers, 1978, Vol. C-27, No. 10, Oct. 1978, pp. 923-926.

19. DIAGNOSTIC ACCURACY AND X-RAY IMAGE PROPERTIES

Kundel, H. L., Revesz, G., Shea, F. J., Ziskin, M. C., Temple University, School of Medicine, Dept. of Radiology, *3322 Broad St., Philadelphia, Pennsylvania*, 19122, United States of America

The objective of this research is to understand the relationship between x-ray image quality and film reader performance.

The pulmonary nodule, frequently a manifestation of primary or metastatic lung cancer and often overlooked on chest films, will be used as a model system.

The relationship between a physical measure that we call conspicuity which is a direct function of nodule size, contrast and edge gradient and an inverse function of background complexity and observer performance will be studied in simulated nodules and in renal pulmonary nodules collected in a clinical study.

The clinical study will compare both detectability using ROC analysis and conspicuity in films made on the same patients at low and high kVp. The relative value of low vs. high kVp in chest radiography will, therefore, be quantitatively determined for lung nodules.

BIBLIOGRAPHIC REFERENCES: Kundel, H.L., Revesz, G. and Toto, L. Contrast gradient and the detection of lung nodules. Invest. Radiol. 14:18-22, 1979. Kundel, H.L. Images, image quality and observer performance. Radiology 132:265-271, 1979.

20. RADIOGRAPHIC IMAGING FOR CANCER DIAGNOSIS

Doi, K., Kirchner, P. T., Metz, C. E., Duda, E. E., Anderson, T. M., MacMahon, H., Patronas, N. J., Kodera, Y., Vyborny, C. J., University of Chicago, Pritzker School of Medicine, Dept. of Radiology, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

The aim of our research is to improve the diagnostic quality of radiographic images for cancer diagnosis and to minimize the patient exposure incurred during the radiographic examination. Our plan includes (1) application of magnification radiography with an ultra high speed rare-earth recording system to chest radiography for the characterization of pulmonary masses (and to distinguish benign from malignant); (2) in bone radiography, development of a high speed and high resolution technique for skeletal radiography to identify bone metastases and to assess disease progression; and (3) evaluation of new stereoscopic techniques for accurate diagnosis of brain tumors. Clinical results will be analyzed by a group of radiologists in blind studies or side-by-side comparisons of radiographs, in order to establish statistically the usefulness of the new techniques applied to various examinations.

The technical approach to applied and clinical studies of radiographic imaging described above is based on the application of methods of optical communication theory to the analysis of factors affecting detail visibility of radiographic images. This involves (1) x-ray energy spectral analysis to study the relationship between the beam quality, patient exposure and image quality; (2) sensitometric evaluation of recording systems; (3) evaluation of modulation transfer functions to provide transfer characteristics of recording systems and of geometric unsharpness; (4) investigation of radiographic mottle to determine the effect of noise on detail visibilities of low contrast radiologic objects; (5) computer simulation studies to optimize the physical parameters discussed above, and (6) ROC analysis of observer performance in detecting simple test object images and in evaluating diagnostic accuracies of bone radiography.

BIBLIOGRAPHIC REFERENCES: Chan, H.P., and Doi, K.: Investigation of scattered radiation in diagnostic radiology by Monte Carlo method. Medical Physics 7: 422, 1980 (abstract). Doi, K., and Chan, H.P.: Evaluation of absorbed dose in mammography: Monte Carlo simulation studies. Radiology 135: 199-208, 1980.

21. OPTIMIZATION OF DIAGNOSTIC X-RAY IMAGING

Johns, H. E., Yaffe, M., Fenster, A., Taylor, K., Ontario Cancer Inst., Physics Division, *500 Sherbourne St., Toronto, Ontario*, M4X 1K9, Canada

OBJECTIVES: a) To optimize present diagnostic X-ray imaging techniques to achieve maximum diagnostic information at minimum radiation risk to the patient. b) To develop new diagnostic X-ray imaging techniques capable of extracting additional information not available with present methods.

APPROACH: a) A variable monoenergetic X-ray source has been constructed. It will be used to measure such parameters of image formation and image quality as sensitivity of X-ray image receptors, spatial resolution and noise. b) The magnitude and distribution of scattered radiation are being measured for various beam geometries for conventional radiology and CT scanning. c) Models are being developed to describe the entire X-ray imaging process. Measured values of sensitivity, resolution, scattered radiation and noise will be used to make predictions of image quality and lesion visibility. Models will allow preliminary image optimization for new techniques involving special X-ray beam filtration or use of novel image receptors. d) New ideas will be tested first with tissue-like phantoms being developed in the laboratory, and later clinically in radiology departments with the cooperation of diagnostic radiologists. e) An investigation of dual energy CT scanning using variable X-ray beam filtration is presently being carried out in an attempt to obtain additional information from CT scans while removing certain spectral artifacts from the images. f) Research into digital projection radiography and fluoroscopy is beginning. An investigation of suitable X-ray detectors for this purpose is now under way.

22. IMAGE RECONSTRUCTION FROM INCOMPLETE PROJECTIONS

Lewitt, R. M., State University of New York, Buffalo Campus, School of Natural Sciences & Mathematics, Dept. of Computer Science, *3435 Main St., Buffalo, New York*, 14214, United States of America

OBJECTIVE: To advance radiological techniques for detection and diagnosis of cancer pathology, with potentially reduced exposure of the patient to radiation, by developing unconventional measurement techniques and associated reconstruction algorithms for computer assisted tomography (CAT).

APPROACH: Methods of X-ray projection data collection will be investigated which involve modified forms of the conventional scanning modes. Projections are usually measured over their complete linear extent, i.e., the measurement field of view includes the entire cross section under examination. However, only a specific region of the cross-sectional image needs to be reconstructed accurately for the detection and diagnosis of some types of early cancer lesions. Hence the X-ray dose to the patient would be reduced, compared to that of conventional CAT, if projection data were accurately measured only for X-rays traversing the cross-sectional region of interest. Parts of the projections which are outside the limited field of view might be measured at low spatial resolution, or not measured at all. The mathematical basis of image reconstruction from such data will be formulated, and practical algorithms will be implemented and evaluated. The performance of various algorithms will be compared using computer-generated projections of realistic simulated phantoms. Measured projection data will be used to determine how these algorithms should be applied in clinical practice.

23. DEVELOPMENT OF SOLID STATE IMAGE RECEPTORS FOR X-RAY IMAGING

Ein Gal, M., Xerox Corp., *300 N. Halstead St., Pasadena, California*, 91107, United States of America

OBJECTIVES: Demonstrate the clinical efficacy of a large area XSEL system based on using induction electrometry for scanning the charge distribution generated by an x-ray flux on a photoreceptor. Identify the modifications required for improving the utilization of the system with respect to low-dose, clinical flexibility and simplified, efficient operation.

24. APPLICATION OF IONOPHORES TO RADIOIMAGING OF TUMORS

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This is part of a broader project. A summary of this subproject is not available.

3. X-RADIOGRAPHY OF THE BREAST AND OTHER BODY SITES

25. PREDICTIVE VALUE OF WOLFE CLASS IN BCDDP WOMEN

Carlile, T., Thompson, D. J., Kopecky, K. J., Gilbert, F. I., Present, A. J., Threatt, B., Virginia Mason Research Center, *1000 Seneca St., Seattle, Washington,* 98101, United States of America

The principal objectives of this study are (1) to evaluate the Wolfe system of breast parenchymal pattern classification for both film-screen and xeromammography, in terms of the relative risks of breast cancer incidence within a period ending 7 1/2 to 10 years after a negative screening examination; (2) to assess the interrelationships of the Wolfe classification with other breast cancer risk factors; (3) to measure the inter- and intra-observer reliability of the Wolfe classification at different levels of observer expertise.

Women enrolled at four Breast Cancer Detection Demonstration Projects will be followed by telephone and letter contacts, in order to identify cases of breast cancer in initially disease-free women; pathology review of all cases will verify the presence of cancer. The initial negative mammograms for each incident breast cancer case (approximately 600-800 are expected), along with those for a random sample of twice as many controls, will be blindly classified according to the Wolfe scheme, and additional risk factor data will be collected on each subject. The data from this case-control study will provide estimates of relative risks of breast cancer associated with Wolfe class taking into account the effects of the other factors. Reliability and consistency of the Wolfe system will be measured. It is expected that information will be obtained that might contribute to an improved determination of the frequency of mammographic screening.

26. CLINICAL DIAGNOSIS OF BREAST CANCER BY XERORADIOGRAPHY

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In order to obtain more accurate diagnoses of breast cancer with less trouble, xeroradiography has been applied in the clinical diagnosis of breast cancer, along with mammography.

The pictures of xeroradiography are taken at the breast in two horizontal and sagittal directions, using the Xerox 125 system created by Fuji Xerox Co.

At present, breast carcinoma is correctly diagnosed 70% of the time by xeroradiography in comparison with 83% by mammography.

More correct clinical diagnosis of breast carcinoma will be brought about by improving exposure factors in xeroradiography.

27. STUDY OF VALIDITY OF CLINICAL EXAMINATION AND X-RAY MAMMOGRAPHY AS SCREENING TESTS FOR BREAST CANCER (ABBREV)

Chamberlain, J., Burn, J. I., Price, J. M., Nathan, B. E., Clifford, R. S., Simpson, P., Inst. of Cancer Research, Division of Epidemiology, *Clifton Ave., Sutton SM2 5PX, Surrey, England, United Kingdom*

The aim of this study is to determine the error rates of clinical examination and mammography in screening for breast cancer and to measure reproducibility between two observers performing the same test. Women over 40 years of age are screened in a well-women clinic where, in addition to a medical history, they have two independent examinations of the breasts, one by a nurse and one by a doctor, and mammography, using the low dose medichrome film system. Mammograms are read independently by two radiologists. Women in whom an abnormality is detected are referred for surgical assessment, biopsied when necessary, and in those in whom cancer is found, follow-up is continued for at least 15 years. To get some idea of the false negative results (the cancers which would be missed by annual re-examination), all women are asked to attend for re-screening at six-month intervals for the first year and then to have one further re-examination two years after initial entry into the study; this, it is hoped, will help determine optimum screening frequency. To date about 6,000 screenings have been done in 2,000 women and 32 cancers found. The economic study is trying to assess both the costs and the benefits of screening. Not only are the health service costs of providing screening taken into account, but also all costs resulting from referral to hospital for surgical opinion and biopsy and costs of treating cancers found. These will be compared with conventional management of breast disease in a system without screening. Benefits are being assessed by trying to obtain a measure of the value which women themselves put on the screening service. It is hoped that eventually some measure of the effectiveness of screening in reducing mortality can also be included.

28. EVALUATION OF PERIODIC BREAST CANCER SCREENING WITH MAMMOGRAPHY AND CLINICAL EXAMINATION

Venet, W., Shapiro, S., Strax, P., Venet, L., Fink, R., Health Insurance Plan of Greater New York, Dept. of Research & Statistics, *625 Madison Ave., New York, New York,* 10022, United States of America

This is a randomized trial designed to test whether periodic screening with clinical and mammographic examinations results in a long-term reduction in breast cancer mortality. Linked to this primary objective are several issues of major importance in assessing benefits to be derived from breast cancer screening, e.g., the relative value of the two screening modalities, ages of women to be screened, periodicity of screening, identification of parameters related to development of the disease, and determinations of underlying cause of death. Approximately 62,000 women, aged 40-64 at the time of entry to the study and allocated to either a study or a control group, are under surveillance. Study women were offered screening examinations; of the 65 percent who accepted an initial examination, a large majority had at least one of the three additional screenings at annual intervals. Control women continued to receive their regular medical care. Screening ended in mid-1970, and follow-up on the entire study and control populations for breast cancer cases and death ascertainment continues. The survival status of all known breast cases through December of 1977 has been established, and no one is lost to follow-up. New data support earlier results on screening benefits. At ten years of follow-up from entry, a 30 percent differential exists between the total study (screenees and refusers) and control group in breast cancer mortality. The impact of the screening program continues to be confined to women 50 years of age and over with no benefit at ages 40-49. Eight-year case fatality rates show similar relationships. The differential between control and study cases is due almost entirely to the low rates among cases detected through screening, with cases detected through mammography alone showing a rate that is exceptionally low. At this point in the study there appears to be strong support for periodic screening at ages of 50 years and over with the two modalities.

29. SCREENING FOR DETECTION OF BREAST CANCER

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Six month renewal of Breast Cancer Detection Demonstration Project. Contractor will rescreen approximately 84 women during the first three months of the renewal period and will perform activities related to report data acquisition, correction, and validation for the entire six month period. Screening will be accomplished through the modalities of mammography and physical examination in accordance with the contract statement of work and the NCI/American Cancer Society guidelines. The end of this renewal period will mark the conclusion of this project which called for the initial screening of approximately 10,000 women and annual screening for four years after the initial screening of as many of the 10,000 women as possible.

30. DETERMINATION OF A RISK LEVEL FOR BREAST CANCER AND ITS APPLICATION TO MASS SCREENING

Bremond, A. G., Rochet, Y., Magnin, G., Hopital Edouard Herriot, Clinique Gynecologique, *Pl. d'Arsonval, 69374 Lyon Cedex 2, France*

Nationwide X-ray screening is both impracticable and unadvisable. If high risk women were identified, this examination could be restricted to a smaller number of patients. On the basis

of known epidemiological data, a double prospective survey can be carried out among cancer-free control women and those who have had breast cancer. The risk level, determined through a computer program, should select 80 percent of women with cancer and not apply to more than 50 percent of controls.

31. BREAST CANCER DETECTION DEMONSTRATION PROJECT

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The Contractor will continue to rescreen as many as possible of an original number of ten thousand women participating in this project. These women wil continue to be rescreened on a projected annual basis by means of three screening modalities - mammography, thermography, and physical examination, in accordance with the contract statement of work and NCI/ACS issued screening guidelines.

32. PROGRAM FOR EARLY DETECTION OF BREAST CANCER

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One year renewal of Breast Cancer Detection Demonstration Project. Continue to rescreen as many as possible of an original number of ten thousand women participating in this project. These women will continue to be rescreened on a projected annual basis by means of three screening modalities - mammography, thermography, and physical examination, in accordance with the contract statement of work, and NCI/ACS issued screening guidelines.

33. NEW FLUORESCENT X-RAY TUBES FOR MAMMOGRAPHY

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Fluorescent radiation from Mo anode tubes is commonly used for film mammography. The quasimonoenergetic radiation at low energy (17-20 KeV) produces good subject contrast. However this low energy radiation does not penetrate well so it produces a high dose. Recent results have indicated that radiation of slightly higher energy (20-20 KeV) might provide adequate contrast, thus permitting imaging at much lower dose.

This study will investigate the fabrication of several 'transmolybdenum' (i.e., Z greater than ZMo) anodes for use in mammography. A demountable x-ray tube has been fabricated which will permit the interchange of several different anode materials. Rhodium and palladium anodes have been constructed by depositing thin film on graphite and copper substrates. Other anodes will be studied. A Si(Li) spectrometer interfaced to a minicomputer will be used to analyze the spectral distribution. Techniques can be adjusted to provide beams of similar spectral purity from the different anodes. This will permit a study of the effect of energy on subject and radiographic contrast.

Thermal loading presents the major problem in these new anodes. The data gathered from the work above should indicate which energies are most promising for mammography. Solutions for the specific elements will be sought. Thermal aging of the demountable anodes can be studied microscopically. Since the anodes can be easily replaced, destructive testing can also be done to determine operating limits. The final goal is to produce a new fluorescent anode tube for mammography with clinically useful output.

34. TEST PHANTOMS FOR OPTIMIZING MAMMOGRAPHIC TECHNIQUE

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There is great need to both minimize patient exposure and maximize visibility of diagnostic details in mammography. A prerequisite to meeting this need is to determine average glandular exposure per view and detail visibility of the resulting roentgenogram, for alternative mammographic systems and techniques. We have previously reported such data, obtained using a simple phantom, and plan to improve on and extend past work. The study involves three aspects: 1. Detail visibility test phantoms. Both sophisticated research and simple versions are planned, for research and routine clinical use, respectively. A greatly improved research model has been developed which permits precise measurement of the visible size of simulated calcific specks and soft tissue fibrils in fat. A special procedure in reviewing roentgenograms assures reproducible readings. 2. Dosimetry. Ionization chamber depth dose measurement methods are being validated, and results will be compared with those obtained using thermoluminescent dosimetry. 3. Measurements. Intercomparison measurements are planned of both detail visibility and depth dose in a D.R. White 'average breast material' BR-12 breast phantom. Systems to be studied include screen-film types, Xerox 125 and Xonics XERG. Where possible, scatter-control and magnification setups will be employed as well as the usual contact exposures.

35. RADIOGRAPHY, PULMONARY FUNCTION AFTER RADIATION THERAPY OF THE CHEST (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

36. DIAGNOSIS OF CANCER OF THE BILIARY TRACT AND PANCREAS BY TRANSCUTANEOUS CHOLANGIOGRAPHY

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OBJECTIVE: To evaluate the usefulness of fine needle cholangiography (Chiba Method) in the differential diagnosis of tumors of the biliary tract and pancreas.

APPROACH: The method described by Okuda, University of Chiba, (known as the 'Chiba Method') is used. Under local anesthesia in the direct intercostal region, a flexible needle, 18 by 0.2 mm, is inserted and then removed slowly while injecting the radiological contrast medium for catheterization of the biliary tract. Once this is done the contrast medium is injected to obtain complete opacity of the entire biliary tract. Numerous radiographic images are obtained from diverse angles to obtain adequate imaging for diagnosis.

PROGRESS: Initially we observed a low margin of correlation between diagnosis and surgical findings. Surgery was performed where indicated. Comparison has been made between surgical and radiological findings. Currently we observe a correlation margin of 80% in comparing radiological and surgical findings. (Translated)

37. ROENTGENOSTEREOPHOTOGRAMMETRY FOR ESTIMATION OF LIVER SIZE IN MALIGNANT DISEASE OF THE LIVER

Bengmark, S., Martensson, H., Fredlund, P., Lunds Universitet, Dept. of Surgery, *Lasarettet, S22101 Lund 7, Sweden*

OBJECTIVE: In treatment of liver tumors there is a need for simple, exact methods to measure variation in tumor and liver size. Selvik has worked out a computerized X-ray technique to determine the three-dimensional positions of radio-pak indicators. This method gives very exact measurement of volumes and shape of liver size and intrahepatic tumor masses. It is tested in patients with liver metastases in order to diagnose liver metastases or to follow the effect of surgical and cytostatic treatment.

APPROACH: In patients with colorectal cancer with or without liver metastases, tantalum-spheres (0,8 mm size) are placed under the liver capsule during surgery. The size and shape of the liver is determined postoperatively by X-ray stereophotogrametric method. This procedure is repeated at regular intervals to diagnose liver metastases and to follow the effect of instituted therapy, liver resection, liver dearterialization and cytostatic infusion on established metastases.

PROGRESS: Our preliminary results show that we can follow the regeneration of the liver very closely after resection, also to the regression of liver volume during the first month after dearterialization. We intend to compare this stereophotogrametric method with computerized tomography.

38. RADIATION-INDUCED MALIGNANCIES DUE TO MASS SURVEY OF THE STOMACH

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Mass X-ray for detection of cancer of the stomach has been widely used in Japan. The study aims to estimate possible risk due to such low level diagnostic exposures. An exposed population with more than 5 million man-years is registered at the Cancer Detection Center, Miyagi Cancer Society, Miyagi Prefecture. Statistical analysis of the exposed population and dosimetry of every individual will be undertaken and the prospective risk of subsequent malignancies will be estimated in rem per man. The non-exposed population of Miyagi Prefecture will be used as a control population.

39. EFFICACY STUDIES OF DIAGNOSTIC X-RAY EXAMINATIONS

Abrams, H. L., McNeil, B. J., Greenes, R. A., Hessel, S. J., Judy, P. F., Mellins, H. Z., Van Houten, F. X., Berenberg, A. L., Jones, B., Peter Bent Brigham Hospital, *721 Huntington Ave., Boston, Massachusetts,* 02115, United States of America

This proposal is designed to determine prospectively the frequency of specific indications for the upper gastrointestinal series (UGI) and the intravenous pyelogram (IVP), the yield of important abnormalities associated with these indications, the sensitivity and specificity of the UGI and IVP, and the diagnostic loss, economic gain and radiation decreases associated with the restricted set of indications. These objectives will be attained and compared in three settings: a teaching hospital, a community hospital, and a health maintenance organization. In all three, a series of forms will be prospectively completed by the referring physician, the examining radiologist, and the research assistant which will detail the indications and pertinent data, record the radiologic diagnosis, and include the clinical and pathologic follow-up and verification. Data will be stored in the computer for a two-year period, and analyzed during the third year. An optimal strategy for clinical use of UGI and IVP will be designed so as to minimize cost and radiation exposure with the least possible loss of important diagnostic information.

40. A SCANNING EQUALIZATION SYSTEM FOR CHEST RADIOGRAPHY

Plewes, D. B., Wandtke, J. C., University of Rochester, School of Medicine & Dentistry, Dept. of Radiology, *601 Elmwood Ave., Rochester, New York,* 14627, United States of America

Chest radiography represents some 40-50 percent of a radiology department's activity and currently suffers from some technical limitations. The large differences in penetration of the chest will cause a proper lung field exposure to underexpose the mediastinum. A large volume of lung tissue is imaged suboptimally due to dense overlying structures of the heart, diaphragm, and spine. Equalization techniques that use specially designed filters to preferentially attenuate the incident x-ray beam over the lung field and produce a more uniformly exposed image prove to be clinically impractical due to the difficulty of designing a good filter to match all patient builds as well as long set up time required for their use. We are proposing a specialized scanning imaging system that will optimally expose all areas of the chest film by measuring the beam attenuation for each point over the patient with an air ionization chamber that will automatically adjust the tube output to compensate for large changes in patient attenuation. We feel this image will allow good lesion detectability over the entire lung volume as well as in the mediastinum at doses that may be 1/2 of those currently used. We propose testing the impact of this unit with lung phantom studies and a small clinical trial.

41. IMPROVED CONTRAST IN CHEST RADIOGRAPHY

Sorenson, J. A., Nelson, J. A., Jacobsen, S. C., Armstrong, J. D., Stanish, W. M., Baxter, B. S., Utah Higher Education System, University of Utah, School of Medicine, Dept. of Radiology, *1400 E. 2nd S., Salt Lake City, Utah,* 84112, United States of America

We will develop and evaluate methods for obtaining improved contrast in chest radiography. Methods for improving contrast will be unsharp masking and efficient scatter rejection, including slit radiography and improved anti-scatter grids. Evaluation will be by contrast measurement, nodule detection experiments, and clinical studies of patients with known or suspected lung disease, including lung cancer and occupational lung disease.

42. DETERMINATION, IN PEDIATRICS, OF THE EXTENT OF CANCER BY MEANS OF LYMPHADENOGRAPHY

Papendieck, C. M., Ostrowski, I., Luis, D. R., Hospital de Ninos de Buenos Aires, Dept. Cirugia, *Gallo 1330, 1425 Buenos Aires, Capital Fed, Argentina*

OBJECTIVES: To determine lymphatic nodal and extranodal involvement in the metastases of tumors in childhood, and the retrograde or anterograde spreading of primitive tumors of the lymphatic system, by means of the transnodal lymphography.

APPROACH: Study of patients from 0-14 years of age registered at CETNI (Centro de Estudio y Tratamiento de los Tumores en la Infancia -Hospital de Ninos) with tumoral pathology, and with the following aims: diagnosis, differential diagnosis, and diagnosis of the degree of extension.

43. THE JOHNS HOPKINS LUNG PROJECT FOR THE EARLY DETECTION, LOCALIZATION AND THERAPY OF LUNG CANCER

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This study began in 1969 when the Johns Hopkins Medical Institution was asked to (1) develop improved methods for the cytological detection of lung cancer, (2) develop improved methods for the localization of lung cancers that are not detectable by chest X-rays, and (3) test these screening techniques in a population sample. The procedures which evolved are now being employed in Phase II of The Johns Hopkins Lung Project and by the other two centers in the Early Lung Cancer Cooperative Study - The Memorial Sloan-Kettering Hospital for Cancer, and Mayo Foundation. The three collaborating centers are assisted in uniform data collection and analysis by the University of Cincinnati. The goal of the cooperative study is to determine the effect of early cytological or X-ray detection, followed by surgical therapy, on long-term survival in lung cancer, as measured by lung cancer mortality in the survey populations. The Johns Hopkins Lung Project has recruited 10,390 male smokers, aged 45 or over, from the Baltimore metropolitan community. Volunteers were randomized into (a) a group screened by annual chest X-ray, and (b) a group screened by sputum cytology in addition to their annual chest X-ray. All chest X-ray examinations include independent double reading. In addition, all sputum cytology screenees receive an annual examination of an aerosol-induced sputum specimen plus an examination of mailed morning sputum every four months. Subjects in whom cancer is detected may be admitted to the Johns Hopkins Hospital for localization and therapy. Curative resection is undertaken where possible, otherwise therapy includes chemotherapy and radiotherapy. All ten thousand subjects will be followed for at least five years to determine survivorship or cause of death.

B. RADIOISOTOPES

1. RADIOISOTOPE SCANNING OF TUMORS

44. EXTERNAL DETECTION OF TUMORS BY RADIONUCLIDE LABELLED IMMUNOGLOBULINS

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To date approximately 150 patients (V.A.) have been examined by scanning with antibodies to carcinoembryonic antigen (CEA), alpha-fetal protein (AFP) and human chorionic gonadotropin (HCG) labeled with I-131. Overall sensitivity of the method is about 80% for tumor detection. This figure could be higher except that the resolution limit of available scanning instrumentation is 1-2 cm. Approximately 40 patients with colorectal cancer, 20 with lung cancer, 20 with other digestive tract (pancreas, stomach, esophagus, etc.) cancer have been studied. Plasma levels of circulating antigen do not affect localization by

scanning. Surgical specimens have consistently demonstrated tumor to non-tumor ratios of radioactivity to be 2.0-2.5.

The Tc-99m labeling of IgG has been developed to the point of clinical evaluation in lymphoscintigraphic procedures for the detection of nodal metastases. Currently used iodination procedures have been examined as well as the suitability of commercial radioiodide from various suppliers. Amersham and Union Carbide provide products suitable for antibody labeling. The chloramine-T procedure was found to provide the most efficacious labeled proteins in regard to reliability, retention of immunological activity, and suitability for patient administration. Presently studies are underway to evaluate In-III labeled antibodies. Initial results indicate that anti-CEA IgG can be labeled with In-III using DTPA as a chelating agent or bridging intermediate.

45. REGIONAL PERFUSION AND VENTILATION IN BRONCHOGENIC CARCINOMA

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OBJECTIVE: To evaluate regional perfusion and ventilation during various stages of development of bronchogenic carcinoma, as well as during and after radiotherapy or chemotherapy.

METHOD: The method used in this study involves a technique employing a system of multiple detectors for the registration of information and Xe-133 in saline solution as a radiotracer. The radiotracer is administered endovenously, thereby allowing for studies of both perfusion and ventilation. In cases where it is deemed convenient, perfusion is also studied by macroaggregates labeled with In-113m and gammagram with rectilinear scanner.

The patients under study are being treated at the Instituto de Oncologia y Radiobiologia and in most cases have bronchogenic carcinoma. The studies are performed on these patients in series during and after treatment, using as a reference the study performed prior to the initiation of treatment.

The information obtained by these studies is complemented with results of other tests such as spirometry, radiologic studies, gasometry, radiocardiography, etc.

PROGRESS: Twenty patients with various stages of bronchogenic carcinoma have been studied during radiotherapy or chemotherapy. No results are yet available regarding patients completing therapy; never the less, results to date indicate the usefulness of this method of follow-up of patients under treatment.

46. RADIOIODINATED CHLOROQUINE ANALOG FOR DIAGNOSIS OF OCULAR MELANOMA

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Thirty-six patients with pigmented ocular lesions originally participated in this study. The early results of the study show that the diagnostic technique used had inadequate specificity. For most patients a clear diagnosis has been made, and their ocular problem resolved. Except for occasional follow-up examinations of some of the patients, work on this project has ended.

47. CANCER STUDIES WITH NEW RADIOACTIVE SCANNING COMPOUNDS

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The objectives of these studies are to identify and investigate the degree of tumor localization, selective organ localization and metabolic rates of specific biologically significant compounds labeled with short-lived nuclides. These labeled compounds will be evaluated as agents for early detection of cancer, will be used to define chemical and biological events leading to carcinogenic reactions and will be studied in normal and abnormal metabolic circumstances. The radionuclides used in the study are all produced in the cyclotron, have short half-lives which greatly reduce patient exposure and require a detection apparatus suitable for high energy radiation. These studies will be evaluated in animals and man with quantitative scanning and imaging systems.

Specific proposed studies in order of priority: 1) Nitrogen-13 Compounds for Tumor and Organ Imaging in Human Cancer Patients; 2) Evaluation of 11C-Amino Acids as Pancreatic Imaging or Tumor Localization Agents; 3) Evaluation of 11C-Thymidine as a Potential Tumor Localizing Agent; 4) In Vivo Disposition of N-13 Labeled Nitrate, Nitrite and Nitrosocarbaryl; and 5) Localization of Soft Tissue Tumors with 73Se-Selenite.

BIBLIOGRAPHIC REFERENCES: Gelbard, A.S., Benua, R.S., Laughlin, J.S., Rosen, G., Reiman, R.E. and McDonald, J.M. Quantitative scanning of osteogenic sarcoma with nitrogen-13 labeled L-glutamate. J. Nucl. Med. 20:782-784, (1979). Gelbard, A.S., Benua, R.S., McDonald, J.M., Reiman, R.E., Vomero, J.J., and Laughlin, J.S. Organ imaging with 13N-L-glutamate. J. Nucl. Med. 20: 663, (1979).

48. SCANNING ACOUSTIC MICROPROBE FOR CANCER DIAGNOSIS

Barber, F. E., Sonnenfeld, M., Sletzinger, L., Harvard University, Boston Campus, School of Medicine, Dept. of Radiology, *25 Shattuck St., Boston, Massachusetts*, 02115, United States of America

A new method has been developed for imaging the fine structure of human tissues called a scanning acoustic microprobe. The system detects, on a scale of a fraction of a millimeter resolution, the isotropic scattering strength, directive scattering strength, directivity, and relative attenuation of tissues at each point in the image plane. By computer graphics an image is reconstructed using these parameters. The method will be used initially for differential diagnosis of breast tumors and for following the course of therapy. The data acquisition system, data processing and pattern recognition system, and the reconstruction system are all based on original and proven concepts for pulse-echo ultrasonic tissue characterization and imaging.

The microprobe should have general applicability to diagnosis in other organs of the body, as well as the breast.

49. METABOLISM OF BONE SCANNING RADIOPHARMACEUTICALS

Russell, C. D., Dubovsky, E. V., Tauxe, W. N., University of Alabama in Birmingham, School of Medicine, Dept. of Diagnostic Radiology, *1919 7th Ave. S., Birmingham, Alabama*, 35233, United States of America

Radioisotope bone scanning is the most sensitive procedure for detecting tumor metastases in bone, and is widely used for that purpose. The radioactive drugs of choice are complexes of Tc-99m with any of several phosphate derivatives. Scan quality is erratic; this problem is attributed to poorly understood differences between one lot of the drug and another, and between individual patients. The reproducibilty of these radiopharmaceuticals is hard to assess, since - despite wide clinical use - their chemical composition and purity have never been established. At least one of them has been shown to be a mixture of uncertain and perhaps variable composition. The component fractions may each have different properties, some desirable and some detrimental. For quality control in the preparation of these agents, and for an understanding of their clinical properties, new radioanalytical methods are needed which are capable of quantitating the individual fractions. We have thus far developed chromatographic methods showing multiple fractions in the bone scanning agent technetium pyrophosphate, and also in the urine of patients who have received this agent. We have also prepared single fractions of this agent in the laboratory. Funding is now sought to explore the clinical implications of this work. We propose to extend our methods to the other major agents, technetium etidronate and technetium medronate; to adapt them to plasma analysis; and to apply them to study the metabolism of bone scanning agents in order to determine the optimum composition. We expect this work to make bone scanning a more reliable means of cancer detection.

50. BONE SCANNING WITH RADIOFLUORINE AND TECHNETIUM

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This is part of a broader project. A summary of this subproject is not available.

51. QUANTITATIVE BONE SCANNING IN CANCER

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This is part of a broader project. A summary of this subproject is not available.

52. ANALOGUES OF 'BREAST SCANNING AGENTS'

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This is part of a broader project. A summary of this subproject is not available.

53. PANCREATIC TUMOR-DELINEATING RADIOPHARMACEUTICALS

Honda, T., Hahnemann Medical College & Hospital, Medical College, Dept. of Radiation Therapy & Nuclear Medicine, *235 N. 15th St., Philadelphia, Pennsylvania*, 19102, United States of America

This is part of a broader project. A summary of this subproject is not available.

2. RADIOISOTOPE IMAGING OF TUMORS

54. EARLY BREAST CANCER - THE USE OF INTERNAL MAMMARY LYMPHOSCINTIGRAPHY

Chaudry, M., Millis, R., Hayward, J. L., Maisey, M. N., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

A study is being conducted to compare the accuracy of internal mammary lymphoscintigraphy, after subcostal injections of 99-technetium antimony colloid, with internal mammary lymph node biopsy performed at the time of mastectomy. If a good correlation between these methods is obtained, lymphoscintigraphy may provide a non-invasive method of assessing the involvement of internal mammary nodes, enabling more accurate staging of breast cancer and perhaps identifying groups of patients requiring adjuvant therapy after initial surgery.

55. RATIONAL DESIGN OF BREAST TUMOR LOCALIZING AGENTS

Katzenellenbogen, J. A., Heiman, D. F., Carlson, K. E., Senderoff, S. G., Kiesewetter, D., Ng, J. S., Landvatter, S., University of Illinois, Urbana-Champaign Campus, School of Liberal Arts & Sciences, Dept. of Chemistry, *Urbana, Illinois*, 61801, United States of America

A large fraction of human breast tumors contain estrogen receptors and, thus, have the ability to concentrate estrogenic substances. In principle, one should be able to utilize this selective uptake mechanism to concentrate a gamma-emitting radiopharmaceutical whose distribution could be monitored by gamma-imaging techniques. Such a procedure would provide a unique, non-invasive diagnostic tool for localizing breast tumors and metastases and determining their receptor content. This project is concerned with the synthesis and evaluation of such receptor-based, selective breast tumor localizing agents.

Halogenated derivatives (fluorine-18, bromine-77 and iodine-123) of various steroidal and non-steroidal estrogens will be prepared. The halogen will be placed at a position consistent with high chemical and metabolic stability and high receptor binding affinity, and the overall structure of the molecule will be designed to maximize its binding selectivity. This will be done by adjusting its structure to optimize its 'binding selectivity index' (BSI), which is defined as the ratio of its binding affinity to the estrogen receptor to its binding affinity to non-specific binding sites.

These compounds will be evaluated in in vitro binding assays to determine their affinity for the estrogen receptor. Those with high BSI values will be prepared in radiolabeled form and their tissue distribution will be determined in immature rats and in mature rats bearing DMBA-induced mammary tumors. Tissue to blood ratios will be determined at various times, and receptor-mediated uptake will be determined by competition with unlabeled estradiol. Rats injected with the compounds prepared in gamma-emitting form will be imaged under a gamma camera.

BIBLIOGRAPHIC REFERENCES: J.A. Katzenellenbogen, K. E. Carlson, D.F. Heiman, and R. Goswami, Receptor-Based Agents for Imaging Breast Tumors: Estrogen Receptor Interactions and Selectivity of Tissue Uptake of Halogenated Estrogen Analogs, J. Nucl. Med., 21, 550-558 (1980). D.F. Heiman, J.A. Katzenellenbogen, and R.J. Neeley, Estrogen Receptor-Based Imaging Agents 1. Synthesis and Receptor Binding Affinity of Some Aromatic and D-Ring Halogenated Estrogens, J. Med. Chem., 23, 944-1002 (1980).

56. RADIOISOTOPE IMAGING IN EARLY DIAGNOSIS AND MANAGEMENT OF MALIGNANT DISEASE AND TUMOR-SEEKING RADIOPHARMACEUTICALS (ABBREV)

Shanta, V., Lakshmanan, A. V., Rajalakshmi, P. K., Cancer Inst., Dept. of Radiotherapy & Physics, *Adyar, Madras 600020, Madras, India*

OBJECTIVE: Prospective study of lymphomas using all available diagnostic evaluation methods, including 67Ga scanning.

APPROACH: The parameters studied are clinical parameters: hematology, marrow studies, biochemical investigations, lymphography, laparotomy and histology. All cases will be evaluated prior to treatment and on completion of treatment after a fixed time interval. The data will be analyzed and correlated to evolve criteria by which involvement of various sites and organs can be diagnosed using the various diagnostic methods listed above.

Sixty-five patients have been studied so far using mainly a 5-inch rectilinear scanner for the isotope investigation. The analysis is in progress and will be reported next year.

57. ENDOSCOPIC LYMPHOSCINTIGRAPHY

Chiu, R. C., Montreal General Hospital, Dept. of Surgery, *1650 Cedar Ave., Montreal, Quebec*, H3G 1A4, Canada

OBJECTIVE: In vivo mapping of lymph nodes and lymphatic drainage patterns from internal organs, and correlation with surgical, pathological findings on lymph node cancer metastases.

APPROACH: Injection of radio-coloids via endoscopes (bronchial and GI) followed by gamma camera imaging. In animal experiments, correlation with lymph node dissection. In patients, correlation with anatomical findings.

PROGRESS: Instruments developed and technique established. More clinical cases needed especially for GI lymphoscintigraphy. This study will further evaluate the efficacy of this technique in the lymphatic drainage of GI tract, correlate with gallium-67 scan for lymph node metastases, and the possible visualization of lymphomas. This is a valuable technique for study of lymphatic pathophysiology in intact animals and patients (i.e., selective site, individual drainage pattern, simple and safe technique.)

58. EVALUATION OF ENERGY INFORMATION IN NUCLEAR IMAGING AND INVESTIGATION OF PROTEIN BINDING OF CATIONIC RADIONUCLIDES BY LACTOFERRIN

Hoffer, P. B., Weiner, R. E., Yale University, School of Medicine, Dept. of Diagnostic Radiology, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

OBJECTIVE: To determine the mechanism by which radionuclides such as 67Ga localize in both tumor and abscess. Specifically, to study the role of lactoferrin in the localization process. Also to improve 67Ga tumor imaging.

APPROACH: We are studying the affinity of 67Ga for iron binding proteins including lactoferrin and transferrin and comparing this binding affinity to that of ferric iron. We are studying lactoferrin content in tumors by immunofluorescence. We are studying binding of 67Ga to siderophores and the effect of siderophores such as Desferal on augmented blood clearance of 67Ga.

59. NUCLEAR TECHNIQUES IN THE DIAGNOSIS OF LUNG CANCER

Franquiz, J., Cardenas, R., Fong, S., Duran, R., Ministerio de Salud Publica, Instituto Nacional de Oncologia y Radiobiologia,

Departamento de Medicina Nuclear, *Calle 29 y E Vedado, Havana 4, Cuba*

OBJECTIVE: Experimental evaluation of nuclear techniques in the diagnosis of lung cancer and the study of its development, by correlation of findings obtained by these techniques with other examinations and definitive diagnosis of patients, in order to incorporate these techniques into the practice of medicine in our country.

METHOD: Dynamic studies by gamma camera selecting regions of interest and functional images of pulmonary ventilation and perfusion in patients with lung cancer in various stages, or in patients with suspect radiologic pictures.

In the same group of patients, determination of serum levels of a lung cancer antigen using a radioimmunoassay technique. Also, in the same patients, detection and quantification of serum levels of trace element using techniques of neutronic activation.

60. STUDIES OF NUCLEAR MEDICINE APPLICATIONS TO ONCOLOGY

Bronskill, M. J., Ege, G. N., Ontario Cancer Inst., Physics Division, *500 Sherbourne St., Toronto, Ontario*, M4X 1K9, Canada

OBJECTIVE: To improve and develop nuclear medicine imaging techniques in oncology and to evaluate their impact on patient management.

APPROACH: a) Radionuclide lymphoscintigraphy is being developed for sites other than internal mammary lymphatics. Computer-assisted quantification, three-dimensional imaging techniques, surgicopathological correlation (with a dog model), radiation dosimetry and improved radiopharmaceuticals are being investigated. b) Improved gray-scale display systems incorporating microprocessor technology are being investigated to optimize detection of lesions in clinical nuclear medicine images. c) A simple, computer-assisted method for the comparative evaluation of diagnostic imaging procedures is being developed. The method yields short-term evaluations appropriate to the rapid evolution of imaging technology and provides some measure of the impact of the results of diagnostic imaging procedures on the management of cancer patients.

61. IMPROVED TUMOR IMAGING IN NUCLEAR MEDICINE

Barrett, H. H., Barber, H. B., Woolfenden, J. M., Silverstein, M. E., Swindell, W., Patton, D. D., Daly, M. J., Donahue, D. J., University of Arizona, School of Medicine, Dept. of Radiology/Optical Sciences, *1501 N. Campbell Ave., Tucson, Arizona*, 85721, United States of America

The overall goal of this program project grant is earlier and more accurate diagnosis of neoplastic lesions by means of nuclear imaging. Project I is concerned with the development of novel modular scintillation cameras, which will offer advantages over conventional Anger cameras in terms of spatial resolution, count rate, and energy resolution. Project II is for continued research into various kinds of coded apertures for gamma-ray image formation. The emphasis here will be on obtaining true three-dimensional reconstructions. Specific research will be performed on reconstruction algorithms, hybrid digital-optical computers, the rotating slit aperture, the Fourier aperture, and multiple pinhole apertures. Project III involves the use of miniature hand-held detector probes to achieve more accurate estimation of the extent of tumor at the time of surgery. The hypothesis to be tested is that intraoperative use of these probes can improve surgical oncological staging by identifying sites of neoplastic involvement that are not clinically evident. Project IV will explore some new ways to display 3D image data. Emphasis will be placed on an interactive CRT display in which the user can tune back and forth through the depth of the object. Project V comprises clinical and psychophysical evaluation of the new techniques being developed in the other projects.

62. 18F-5-FLUOROURACIL IMAGING IN PATIENTS WITH CANCER

Polcyn, R. E., Lieberman, L. M., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Nuclear Medicine Service, *2500 Overlook Ter., Madison, Wisconsin*, 53705, United States of America

PROJECT OBJECTIVES: (1) To develop 18F-fluorouracil as a tumor scanning agent in selected patients with cancer. (2) To study patients with 'singles' and 'double' photon emission techniques to obtain tomographic images.

PLAN: We will produce radioactive fluorine gas (18F-19F) on the University of Wisconsin van de Graff accelerator and synthesize 18F-FU. Patients with histologically proven cancers will be imaged with a tomographic scanner based on 'singles' detection, and either an emission computerized axial tomographic scanner (ECAT) or a dual head positron camera based on detecting positron annihilation photons in coincidence.

METHODOLOGY: We will inject IV one to five mCi of 18F-FU in 30-60mg of FU in patients referred by the Oncology and Radiotherapy Services. At two hours post-injection the patient will be imaged with one of two tomographic devices and the imaging will be repeated with a second tomographic device if count rates are satisfactory.

RESULTS TO DATE: We have studied 17 patients with cancer using a rectilinear scanner and seven have shown positive images in the region of their tumors. One patient was studied with a dual head positron camera and a lesion in the right anterior cervical region imaged. Continued studies in patients with cancer may lead to a new improved tumor imaging agent.

63. INDIUM-111 CHLORIDE FOR BONE MARROW IMAGING

Coupal, J. J., DeLand, F. H., Kim, E. E., Domstad, P. A., Choy, Y. C., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *Leestown Pike, Lexington, Kentucky*, 40507, United States of America

OBJECTIVE: To evaluate the efficacy of Indium-111 chloride as a bone marrow imaging agent.

PLAN: Two to three mCi of 111In chloride will be administered intravenously to patients. Whole-body imaging will be performed by gamma camera at 24, 48 (and possibly 72)hrs postinjection to determine areas of lessened bone marrow uptake of radionuclide, indicating areas of metastases or diagnosis of diseases related to erythropoiesis such as aplastic anemia. The nuclear medicine physician will interpret scan results and report them to referring physician.

64. SKELETAL IMAGING WITH RADIOISOTOPE AGENTS

Sauerbrunn, B. J., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Nuclear Medicine Service, *50 Irving St. N.W., Washington, District of Columbia*, 20422, United States of America

A retrospective review has now been completed of the use of bone scintigraphy using Tc 99m labeled phosphates in patients with small cell carcinoma of the lung with respect to staging, follow-up, and therapeutic response to chemotherapy. A paper covering these aspects will soon be forthcoming. The collaborators on this study include Doctors Levenson, Sauerbrunn, Ihde, and Minna.

65. MELANOMA DETECTION WITH RADIOPHARMACEUTICALS

Atkins, H. L., Packer, S., Wolf, A. P., Lambrecht, R. D., Christman, D., Fairchild, R., Brookhaven National Lab., *Upton, New York*, 11973, United States of America

The clinical usefulness of the melanin-seeking radiopharmaceutical iodine-123 DMQ (4,3 dimethylamino-propylamine-7-iodoquinoline) is being determined. Specifically, we are looking at patients with malignant ocular (choroidal) and skin melanomas.

New detection devices include: 1) a dual pinhole eye collimator for use with a gamma camera, 2) a two eye-probe counting system (this allows simultaneous counting of 2 eyes), and 3) an ultrasound guided gamma probe (on loan from the University of Michigan). Large melanomas (1000 mm3) have been imaged but we do not know the limitations of the systems mentioned above, since too few patients have been studied. Patients are also being similarly studied with gallium-67 citrate.

Laboratory investigations into the role of melanoma-localizing agents pre- and post-irradiation continue. We are using the Greene malanoma in the rabbit and gallium-67 citrate before and after irradiation with iodine-125.

Our immediate goal has been to find a non-invasive method of determining the presence of an intraocular (choroidal) melanoma and then to evaluate the effects of radiotherapy

and/or hyperthermia with melanoma-seeking radiotherapy and/or hyperthermia with melanoma-seeking radiopharmaceuticals.

66. PROGRAM IN RADIONUCLIDE STUDIES OF TUMORS AND GROWTH

Spencer, R. P., Hosain, P., Sripada, P. K., Banerjee, S. N., Emran, A., University of Connecticut, Health Center, School of Medicine, Dept. of Nuclear Medicine, *Farmington Ave., Farmington, Connecticut*, 06032, United States of America

The study proposes to use conventional and newly developed radiopharmaceuticals to study both tumor growth and the response to medication. Results are checked against models evolved to describe these events. An active area of work is the elucidation of the necessary and sufficient conditions for various radiopharmaceuticals to exert an action or uptake in normal and neoplastic tissue. Thus, multiple analogues have been synthesized of bone imaging agents in order to determine the spatial and charge restrictions on their uptake. The effects of hormonal therapy are being studied on bone scans in men with prostatic carcinoma treated with diethylstilbestrol, and in women with metastatic breast carcinoma under therapy with tamoxifen. Synthesis of several new radiopharmaceuticals has been accomplished, in an effort to examine active sites of enzymes through the use of radiolabeled substrates or analogues.

67. SCANNING ACOUSTIC MICROPROBE FOR CANCER DIAGNOSIS

Barber, F. E., Sonnenfeld, M., Sletzinger, L., Harvard University, Boston Campus, School of Medicine, Dept. of Radiology, *25 Shattuck St., Boston, Massachusetts*, 02115, United States of America

The summary for this project is under entry no. 48.

C. ULTRASONOGRAPHY AND THERMOGRAPHY

68. ULTRASONIC COMPUTED TOMOGRAPHY OF BREAST CANCER

Carson, P. L., Banjavic, R. A., Scherzinger, A. L., Meyer, C. R., University of Colorado, Health Sciences Center, School of Medicine, Dept. of Radiology, *4200 E. 9th Ave., Denver, Colorado*, 80262, United States of America

This proposal is a supplement to NIH Grant #1 RO1 CA25323-01, which was awarded for three years beginning April 1, 1979. The existing grant was funded primarily to provide a clinical evaluation of ultrasonic computed tomography of attenuation and velocity in the breast as a method of diagnosing cancer. Those clinical trials are now under way and progressing well with system improvements promised in the proposal for that grant.

The primary purpose of this supplemental proposal is to develop and evaluate attenuation images that provide an accurate measure of the attenuation coefficient as a bulk property of the tissue. While the present edge enhanced images increase detectability of lesions in some cases and contribute to the diagnosis in combination with the velocity images, it is very important that a more quantitatively and spatially accurate attenuation image be developed and included in the clinical trials. The new attenuation images will be obtained with a phase independent array and a simple, new signal processing. The new imaging technique will be operating reliably for full clinical trials no later than 18 months after the initiation of the supplemental effort. In the remaining 15 months of the supplement, at least 75 patients with a high probability of developing breast cancer will be imaged with new and existing UCT techniques for comparison with pulse echo images, mammography and histologic findings. The phase insensitive array technique and other new methods proposed by this group and others for attenuation and velocity UCT imaging will be compared. These various signal processing techniques will be implemented digitally for evaluation on the same few sets of data from realistic test objects and breast tissue samples. In addition, methods proposed for reconstruction of velocity images from backscatter data will be evaluated using the same test object.

69. BREAST TUMOR DIAGNOSIS BY COMPUTED ULTRASOUND

Swindell, W., Haber, K., Finette, S., University of Arizona, School of Medicine, Dept. of Radiology, *1501 N. Campbell Ave., Tucson, Arizona*, 85721, United States of America

The research applies machine recognition methods to the problem of differentiating between different classes of breast tumors using pulsed echo ultrasound information. We use a commercial water-coupled breast scanner interfaced to a PDP 11-34 computer. We are searching for characteristic features in the echoes from the tumor region that will permit the identification of the tumor type with a high degree of confidence. The features being examined include a) simple statistical quantities derived from the gray-scale histogram such as bin ratios and the various distribution moments; b) texture measurement parameters such as are derived from a min-max analysis or Markov modelling of the signal; c) parameters that quantitatively describe observable features in the image such as retro-tumor enhancement or shadowing and d) features derived from a power spectral analysis of signal.

70. DETECTION OF BREAST CANCER BY ULTRASONIC DOPPLER BLOOD FLOW SIGNALS

Wells, P. N., Halliwell, M., Bristol General Hospital, Dept. of Medical Physics, *Bristol BS1 6SY, England, United Kingdom*

OBJECTIVE: To determine the feasibility of developing a rapid scanner for screening for breast cancer by the ultrasonic detection of abnormal blood flow.

APPROACH: Preliminary experiments have demonstrated that the abnormal blood flow, associated with malignant tumor neovascularisation, produces characteristic ultrasonic Doppler singnals. The possibility of detecting these signals in breast cancer by means of an automatic water-bath-coupled ultrasonic scanner is being investigated, and the physics of the origin of the signals is being studied.

PROGRESS: A library of breast Doppler signals is being collected, using a hand-held skin-contact probe. Methods of characterizing the singnals, including frequency spectrum analysis, are being investigated. A two-dimensional pulse-eco breast scanner is being constructed.

71. USE OF ULTRASOUND IN THE DIAGNOSIS OF BREAST CANCER

Taylor, K. J., Peck, D., Yale University, School of Medicine, Dept. of Radiology, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

A new ultrasound scanner is available which combines automation with high resolution and digital format for display. Financial support is requested to perform a clinical evaluation of this instrument. It is proposed that we scan at least 2500 women over a period of two years. These results will be compared with the xeroradiographic findings, clinical examination and surgical and pathological follow-up in patients proceeding to surgery. This will enable us to determine both the sensitivity and specificity of ultrasound examination of the breast compared with conventional imaging methods and clinical examination. It is also proposed that the acoustic parameters of normal and abnormal tissue will be quantized using computerized facilities which will be available by late 1978.

The advantages of ultrasound imaging are its lack of ionizing radiation, its non-invasiveness, and its capacity, not yet fully exploited, to obtain high resolution in superficial organs. We believe that this project will help to realize the earlier diagnosis of breast disease without the use of ionizing radiation.

72. BREAST DIAGNOSIS - QUANTITATIVE IMAGING BY ULTRASOUND

Greenleaf, J. F., Mayo Foundation, Ultrasound Research Laboratory, *200 1st St. S.W., Rochester, Minnesota*, 55901, United States of America

The goal of this proposal is to investigate methods and techniques for reliable ultrasound scanning to obtain quantitative images of several acoustic parameters within two-dimensional cross sections of the breasts of patients in a period of a few minutes. The instrument will synergistically combine these quantitative multimodal images to obtain diagnosis of breast disease. Ultrasound computer-assisted transmission tomography will be utilized to obtain quantitative cross-sectional images of

acoustic speed, acoustic attenuation, acoustic absorption and scatter and reflection where appropriate. Both analytic and iterative methods of correcting aberrations in the images caused by inhomogeneous refractive index will be investigated. A clinical scanner will be built in which patients scheduled for surgical biopsy will be scanned and the resulting images compared to the histological results of biopsy and/or surgical mastectomy. Comparisons between surgical specimens and acoustic images will be made using methods of automated computer-assisted pattern classification and recognition combined with histologic methods of tissue preparation specifically designed to aid in comparing with ultrasound images of the coronal plane of the intact breast with similar planes through the excised breast. This parallel investigation of the clinical instrument and imaging method, the tissue analysis techniques, and the pattern recognition programs should result in complete evaluation of a prototype clinical instrument capable for use in the high volume clinical environment.

BIBLIOGRAPHIC REFERENCES: Kenue, S. K. and Greenleaf, J. F.: High speed convolving kernels for CT having triangular spectra and/or binary values. IEEE Transactions on Nuclear Science, NS-26(2):2693-2696 (April) 1979. Kenue, S. K. and Greenleaf, J. F.: Efficient convolution kernels for computerized tomography. Ultrasonic Imaging, 1:232-244, 1979.

73. USE OF ULTRASONOGRAPHY TO ESTABLISH TYPE IN HEPATIC TUMORS

Lecuna, V., Avella, J., Hospital Universitario de Caracas, Servicio de Gastroenterologia, *Caracas, Venezuela*

OBJECTIVES: To determine the usefulness of ultrasonography in determining tumor type in hepatic tumors; and to determine the relationship between ultrasonographic characteristics and alterations during treatment.

APPROACH: B mode equipment (static) operating in real-time and with a grey scale. Patients come from the Gastroenterology Service of the Department of Surgery, of the Comision de Linfoma y Unidad de Hematologia y Oncologia Medica.

PROGRESS: To date, 130 patients with a definitive diagnosis of cancer have been studied. Of those, 14 have undergone medical therapy. Thirteen patients with lymphoma have been studied. Although a registry is being kept of the ultrasonographic characteristics, no correlation with the histologic type of the tumor has yet been made. (Translated)

74. ULTRASOUND IN LIVER DISEASE DIAGNOSIS

Youssef, M., Oulu University Central Hospital, Dept. of Radiology, *Kajaanintie 51, 90220 Oulu 22, Finland*

The goals of this project are: 1) To evaluate the accuracy of grey scale ultrasound in defining liver metastases, their different echographic patterns and how to differentiate them from hepatomas, abscesses or even cysts. 2) To answer the following question: Can the different echographic patterns in liver metastases be suggestive of the site of a primary tumor? 3) To follow up the effect of treatment with chemotherapy on the echographic patterns in liver metastases.

75. TRANSPELVIC ULTRASOUND EVALUATION OF THE PROSTATE

Pulestant, A. M., Vine, H. S., Beth Israel Hospital, Dept. of Radiology, *330 Brookline Ave., Boston, Massachusetts*, 02215, United States of America

There are several well-recognized, non-invasive methods by which the prostate may be examined for carcinoma. These include clinical assessment by transrectal palpation, radiographically, and indirectly by measuring serum acid phosphatase. With the recent advances in ultrasound imaging technology, the whole prostate can now be demonstrated through the acoustical pattern generated. The investigators wish to evaluate the accuracy of a gray scale ultrasound examination, which is commonly available in most hospitals for; a. detecting the presence of early prostate cancer, b. calculating the size of the gland, and c. assessing its use in followup of patients on treatment for prostate cancer.

One hundred consecutive adult males who will undergo a prostatectomy or prostatic biopsy will be subjected to an ultrasound examination. The study will be analyzed in conjunction with the pathological report and correlation attempted.

76. RECTAL CARCINOMA - IMAGING STUDY

Thompson, W. M., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Radiology Service, *508 Fulton St., Durham, North Carolina*, 27705, United States of America

The summary for this project is under entry no. 12.

77. ULTRASONIC EVALUATION OF OCULAR TISSUES

Lizzi, F. L., Feleppa, E. J., Greensbaum, M., Herbst, J., Rosenberg, S., Jaremko, N., Riverside Research Inst., Biomedical Engineering Laboratory, *80 W. End Ave., New York, New York*, 10023, United States of America

The overall objective of the present program is to provide the comprehensive improvements in opthalmic diagnosis and treatment monitoring which are needed to permit the optimal use of current and future therapeutic methods. The program is exploring advanced ultrasonic spectrum analysis techniques and testing them for reliability in a working clinical system. The objective is to attain specificity of tissue diagnosis utilizing non-invasive ultrasonic methods. Characteristic histologic features are being assessed by 'signatures' involving several sets of ultrasonic parameters. Precision of tissue characterization will enable detection and identification of a broad class of disorders including, most importantly, intraocular and orbital tumors. Tissue signatures are being determined from an advanced ultrasonic diagnostic system using minicomputer technology and digital processing techniques including deconvolution and cepstrum analysis.

A computer library of these spectral parameters is being developed to serve as the focal point of efforts to identify sets of characteristics associated with specific diseases. Concurrently, experience gained with on-line clinical processing is being used to formulate techniques and diagnostic protocols which will allow the most efficacious use of these signatures in arriving at diagnostic decisions.

The research is a collaborative effort of clinical and engineering staffs. Engineering efforts have been and will continue to be performed at Riverside Research Institute. The clinical studies studies will be performed at the Dept. of Ophthalmology, Cornell University Medical College.

BIBLIOGRAPHIC REFERENCES: Lizzi, F.L., Coleman, D.J., Franzen, L., and Feleppa, E.J., Use of a Spectrum Analysis System for Characterization of Malignant Melanoma, Ultrasound in Medicine, Vol. 4, ed. D. White and E.A. Lyons, Plenum Press, New York, pp. 559-562, 1978. Lizzi, F.L., Coleman, D.J., Driller, J., Franzen, L.A., Jakobiec, F.A., Experimental Ultrasonically Induced Lesions in the Retina, Choroid and Sclera. Invest. Ophthal. 17:350-360, 1978.

78. ULTRASOUND IMAGING AS AN ADVANCED AID IN THE RADIOTHERAPY DEPARTMENT

Whipp, E. C., Orr, J. S., Leeman, S., Blake, P. R., Sutton, P., University of London, Royal Postgraduate Medical School, Dept. of Medical Physics, *Du Cane Rd., c/o Hammersmith Hospital, London W12 0HS, England, United Kingdom*

OBJECTIVES: (a) To improve the accuracy of radiotherapy planning; (b) to assess the accuracy of the initial plan and check patient set-up throughout a course of radiation treatment; (c) to investigate techniques for following tumor development at frequent intervals.

APPROACH: Use of ultrasound imaging and advanced signal processing techniques on ultrasound echoes from tumors.

PROGRESS: Ultrasound has been used for radiotherapy planning at the Hammersmith Hospital for the past 4 years; the other objectives are being implemented through the recent acquisition and development of modern digital imaging and processing equipment.

79. DEVELOPMENT OF ULTRASONIC ENDOSCOPIC PROBES

Green, P. S., S R I International, *Box 3741, San Juan*, 00936, Puerto Rico

Clinical trials are to begin in the second year of the project. Originally, those trials were to have been conducted at the University of California at San Francisco. However, two key staff members have left the University. As a result, the trials will be moved to the Mayo Clinic. A second endoscope system will be built so that development can continue at SRI while experiments are in progress at the Mayo Clinic. Animal experi-

ments with the endoscope will be carried out before examinations of human subjects begin.

80. DEVELOPMENT OF CONTRAST AGENTS FOR ULTRASONIC DIAGNOSIS

Maklad, N. F., University of Kansas, Medical Center, School of Medicine, Dept. of Radiology, *39th St. & Rainbow Blvd., Kansas City, Kansas*, 66103, United States of America

The specific goal of this proposal is to demonstrate the feasibility of detecting small tumors utilizing diagnostic ultrasound techniques with the aid of ultrasonic contrast agents. The tasks necessary to achieve this specific goal are: To identify and develop materials which are tumor specific and which also alter the ultrasonic characteristics of tissue. To determine the ultrasonic properties of selected materials and the differential uptake of selected materials in animal tumor models; To conduct appropriate clinical studies in order to characterize normal tissue, benign disease, and malignant neoplasia by ultrasound, and to compare the results obtained by the ultrasonic method to those of other diagnostic modalities including conventional x-rays (with and/or without contrast) and computerized tomography; to correlate all the results with the pathological specimen evaluation.

81. ACOUSTOSPECTROGRAPHY OF NEOPLASMS

Thijssen, J. M., Verbeek, A. M., Cloostermans, M., Katholieke Universiteit Nijmegen, Sint Radboudhospital, Dept. of Ophthalmology, *6500 HB Nijmegen, Netherlands*

OBJECTIVE: The short-term goal of this project is the improvement of ultrasonographic tumor diagnosis. The long-term goal is the development and subsequent introduction into clinical diagnosis of acoustospectrography. This is a technique of analysis of the RF echograms by means of digital computer programs and which is intended to reveal acoustic parameters of tissues, such as attenuation, reflectivity, acoustic refraction index, acoustic impedance.

The generalization of current and new methods from ophthalmological diagnosis to other disciplines will be emphasized. Early detection of focal lesions as well as the differential diagnosis of diffuse lesions may be greatly improved.

APPROACH: The present state of our research is that we have reached the stage of in vitro and in vivo assessment of the usefulness and applicability of characterization of membranes and tissue transitions. Another approach has been a feasibility study of the in vitro (liver) estimation of the acoustic tissue transfer function (acoustospectrography). The results produced so far yield a positive answer and the research will be extended to other healthy tissues and to tumor tissues.

The acoustical aspects of ultrasound interaction with biological tissues will be further investigated. For that purpose a device will be constructed to measure accurate field plots. A tissue model simulation by a digital computer program will be adapted to a more realistic configuration by using the field measurements.

PROGRESS: A feasibility study on the characterization of tissue membranes and transitions has been successfully performed. The deconvolution procedures employed yielded, also in in vivo measurements, an improvement of the band width and, therefore, of the range resolution by a factor of two. The differentiation of vitreous membranes in the eye from retinal and choroidal detachments may be greatly improved. The in vitro experiments on the estimation of the acoustic tissue transfer function yielded a positive answer as regards the accuracy that can be obtained; therefore, a first and important step towards in vivo application of the technique has been made.

82. COMPUTED DIAGNOSTIC ULTRASONOGRAPHY AND THERAPEUTIC ULTRASOUND ELECTRON MICROSCOPIC CORRELATIONS

Coleman, D. J., Cornell University, Medical Center, New York Hospital, Dept. of Ophthalmology, *1300 York Ave., New York, New York*, 10021, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

83. ULTRASOUND IMAGING AND MEASUREMENTS IN RADIATION ONCOLOGY (HUMAN)

Zagzebski, J. A., University of Wisconsin, Madison Campus, Medical School, Dept. of Human Oncology, *450 N. Randall Ave., Madison, Wisconsin*, 53706, United States of America

This is part of a broader project. A summary of this subproject is not available.

84. PLATE THERMOGRAPHY - BREAST CANCER RISK AND PROGNOSIS

Sterns, E. E., Queen's University, Dept. of Surgery, *King St. W., Kingston, Ontario*, K7L 3N6, Canada

OBJECTIVE: To identify the value of plate thermography as a determinant of prognosis in patients with proven breast cancer and to indicate the potential for breast cancer development in patients who are clinically normal at the time of examination.

APPROACH: Plate (liquid crystal) thermography is used in two groups of patients: 1) immediately prior to biopsy in those with suspected breast carcinoma and 2) in patients seen in the Breast Clinic with a variety of benign and malignant breast problems. The thermograms are interpreted in three categories based on the temperature range and the heat pattern distribution. The patients who have proven breast cancer are followed to determine their survival, measuring the disease-free interval, site and extent of metastases when first discovered, total duration of survival and extent of disease at death. The prognosis will be related to the thermographic classification.

In patients without malignant disease who are post-menopausal the risk of developing cancer will be assessed in relation to the various thermographic rankings.

85. NONINVASIVE SENSING OF SUBCUTANEOUS TEMPERATURES

Barrett, A. H., Myers, P. C., Massachusetts Inst. of Technology, School of Science, Dept. of Physics, *77 Massachusetts Ave., Cambridge, Massachusetts*, 02139, United States of America

This proposal seeks to technically develop and clinically evaluate microwave thermography, a relatively new, safe, noninvasive method in the area of diagnostic radiology. The development and evaluation will be applied to the detection of breast cancer. The frequencies to be used are 1, 2, 3, and 6 GHz, in continuation of previous work indicating true positive detection rates superior to those of infrared thermography and comparable to those of mammography. At these frequencies microwave thermography can sense a temperature change of approximately 0.1 degree C at a depth of several cm with resolution of approximately 1 cm2. The techniques to be developed or investigated are (a) reflection-compensating radiometry, which measures both temperature and emissivity; (b) multimode antennas, which form beams of different resolution; and (c) correlation interferometry. The clinical evaluation programs include clinical trials of these techniques; and trials detected toward determination of (a) the most effective frequency, (b) the ability of microwave thermography to detect small tumors; (c) the ability of microwave thermography to detect tumors in young women; (d) whether microwave thermography may be useful in a screening program which reduces the number of women exposed to X-rays; and directed toward (e) construction, for the first time, of microwave images to be compared with other diagnostic images.

BIBLIOGRAPHIC REFERENCES: A.H. Barrett, P.C. Myers, and N.L. Sadowsky, Microwave Thermography: Application to the Detection of Breast Cancer, pp. 375-385, Prevention and Detection of Cancer, Part II, Detection, edited by Herbert E. Nieburgs, Marcel Dekker Inc., New York, N.Y. 1978.

D. NMR IMAGING AND OTHER RADIOLOGIC STUDIES

86. IMAGING OF THE HUMAN BODY BY NUCLEAR MAGNETIC RESONANCE

Mallard, J. R., Hutchison, J. M., Foster, M., Edelstein, W., Ling, R., Medical Research Council, Dept. of Bio-Medical Physics & Bio-Engineering, *Aberdeen, Scotland, United Kingdom*

OBJECTIVE: To image transverse cross-sections anywhere in the human body, displaying simultaneously, but separately, water concentration (i.e., concentration of hydrogen proton spins) and the spin lattice relaxation time T1 of the proton spins. T1 is related to the closeness of the binding of the water to macromolecules such as proteins. Such images may display abnormalities of water level and water function due to pathology.

APPROACH AND PROGRESS: Using a resistive electromagnet, and a system of orthogonal pulsed magnetic fields, combined with pi and pi/2 pulses of radiofrequency (1.7 MHz) transverse section images made up of 40 lines per frame have been achieved on humans in 8 minute exposures. Measures to reduce heart beating movement artifacts are being introduced together with better systems of determining T1 images.

During the same period since 1973 a considerable biological program has shown the normal pattern of T1 distribution in animals, the range of T1 values for normal tissues being fivefold from 150 msec to 800 msec. Malignant tissues give longer T1 than the corresponding normal tissue and calculations show that this method of imaging may be particularly valuable for imaging breast tumors and secondary tumor deposits in the liver. The reaction of host tissue to an implant of Yoshida sarcoma in the rat also elevates the T1 value in tissuing surrounding the tumor implant. It is believed that the NMR imaging technique may be of great value im imaging pathology other than tumors, particularly that giving rise to abnormal fluid pools, inflammation and changed water characteristics.

87. DEVELOPMENT OF NMR SPIN MAPPING IN MEDICINE

Andrew, E. R., Moore, W. S., Hawkes, R. C., Holland, G. N., University of Nottingham, Dept. of Physics, *University Park, Nottingham NG7 2RD, England, United Kingdom*

OBJECTIVE: To evaluate the technique of NMR spin mapping, developed in the applicants' laboratory, as a method of medical imaging, and to pursue clinical applications.

APPROACH: With the aid of an earlier project grant an intermediate size NMR imaging system was constructed and some excellent images have been obtained of small animals, and the human hand, wrist, and forearm. The growth of an implanted hepatoma D23 tumor within the peritoneal cavity of a live rat was demonstrated. A whole-body NMR imaging system has been constructed, with financial assistance from the Wolfson Foundation, and the first results are now being obtained. Clinical evaluation of these instruments in collaboration with the University of Nottingham Medical School is being pursued, and this includes the detection and discrimination of cancerous tissue.

88. THE APPLICATION OF NUCLEAR MAGNETIC RESONANCE IMAGING IN ONCOLOGY

Bakker, C. J., Schipper, J., Van Peperzeel, H. A., State University Hospital, Dept. of Radiotherapy, *Catharijnesingel 101, 3511GV Utrecht, Netherlands*

OBJECTIVE: The objective of this pilot study is to undertake an exploratory survey of the potentialities of NMR tomography in oncology, in particular with respect to tissue characterization, tumor localization and evaluation of response to treatment, and to make a comparison between NMR tomography and other diagnostic modalities, e.g., computerized tomography.

APPROACH: A state-of-the-art report on NMR tomography will be drawn up from the literature and in consultation with investigators and research groups in the field. Whole-body and small-scale NMR imaging experiments will be performed in collaboration with Philips' Medical Systems Division at Eindhoven and the University of Technology at Delft.

89. EVALUATION OF HIGH FIELD MEDICAL NMR IMAGING

Goldberg, S. J., Hilal, S. K., Cho, Z. H., Kelcz, F., Moudsley, A. A., Seaman, W. B., Hall, E. J., Geard, C. R., Miller, R. C., Columbia University, College of Physicians & Surgeons, Dept. of Radiology, *630 W. 168th St., New York, New York,* 10032, United States of America

The aim of this program project is to evaluate a high magnetic field strength clinical NMR imaging spectrometer. The apparatus may be operated at 15kG, thus permitting the imaging of protons, sodium and phosphorus. The clinical evaluation will be carried out on cancer patients with the confirmed diagnosis or strongly suspected diagnosis of a malignant neoplasm with poor prognosis. The research involves physical experiments to optimize imaging parameters and develop methodology for calibration and quality control of this new modality. In vitro NMR experiments are planned on resected tissues to permit a correlation between the clinical images and actual measurements obtained directly from the resected tissues. The clinical correlations are between x-ray CT and NMR images obtained at similar anatomical levels for both proton and sodium nuclei. It is hoped that this modality will provide unique information about tissue characteristics in vivo, thus increasing the probability of noninvasively reaching a specific diagnosis. The safety of this new modality will be studied at the systemic level and at the cellular level. We hope to correlate the biological hazards of NMR and ionizing radiation. Blood flow measurement will be carried out noninvasively using the clinical NMR spectrometer in the carotid artery in the neck and in cross-sections of the brain. We will study the optimal NMR imaging technique, image artifacts and reconstruction algorithms on an off-line satellite computer. The study of phosphorus in the human body will be carried out in selected areas of normal and pathological human tissue nonivasively, in a clinical setting, with correlation with animal results.

90. EPR STUDIES ON DETECTION AND TREATMENT OF CANCER

Zimbrick, J. D., Stephens, R., Baker, L., Dean, D., Jewell, W., Mathew, A., University of Kansas, Lawrence Campus, School of Liberal Arts & Sciences, Dept. of Radiation Biophysics, *112 Bailey Hall, Lawrence, Kansas,* 66045, United States of America

Electron paramagnetic resonance (EPR) spectroscopy is being evaluated for use as a potential screening technique for early detection of cancer. EPR spin labeling techniques are being utilized to elucidate possible membrane and intracellular viscosity changes which may occur in blood components of humans with cancer. A double-blind study will be continued on the EPR signal intensity of Cu(plus plus) bound to ceruloplasmin (Cu(plus plus)-Cp) and on the ratio Cu(plus plus)/total Cu in serum samples from female volunteers who are asymptomatic but have a higher than average risk of developing breast cancer. Animal tumor model systems already developed will be utilized to provide lymphocytes for spin labeling studies to determine possible changes in membrane fluidity or cytoplasmic viscosity associated with cancer. These tumor models will also be studied to determine how soon after tumor cell implantation the changes in Cu(plus plus)-Cp level and in the ratio Cu(plus plus)/total Cu occur, and to obtain more information on possible hypotheses for these changes. Studies on the molecular properties of CP, including single crystals of CP, will be continued. These will include electron spin echo studies which may help to characterize the binding sites of Cu in the molecule.

BIBLIOGRAPHIC REFERENCES: Horn, R. A., E. J. Friesen, R. L. Stephens, W. R. Hendrick, and J. D. Zimbrick, Electron Spin Resonance Studies on Properties of Ceruloplasmin and transferrin in Blood from Normal Human Subjects and Cancer Patients, Cancer 43 (6), 2392-2398 (1979).

91. DEVELOPMENT OF RADIOGRAPHIC TEACHING MATERIALS ON ASBESTOS FOR PHYSICIANS

Merchant, J., U.S. Dept. of Health & Human Services, Public Health Service, Center for Disease Control, National Inst. for Occupational Safety & Health, *944 Chestnut Ridge Rd., Morgantown, West Virginia,* 26505, United States of America

OBJECTIVES: This interagency agreement supports the preparation of a teaching module with an emphasis on the roentgenographic manifestations of asbestos related disease. This agreement will be part of an ongoing contract between the American College of Radiology and the National Institute of Occupational Safety and Health which has produced teaching materials for the Coal Miners' Black Lung Program. This module on asbestos related lung disease will help achieve one of the primary goals of the Division of Cancer Control and Rehabilitation, National Cancer Institute; i.e., the assistance of health professionals in the application of new and available knowledge

and technologies to improve the diagnosis and treatment of cancer.

ACCOMPLISHMENTS: The module, which is nearing completion, consists of a written text describing the clinical manifestations, epidemiology, pathology and roentgenology of asbestosis. Associated tables, photographs, slides and radiographs illustrate the text. Case descriptions accompany the radiographic reproductions and slides. Thirty full-size chest x-rays show asbestos related disease including lung cancer and mesothelioma. Instruction in the utilization and application of the International Labor Organization's classification system is also given. A sample classification is completed for each film in the set.

PLANS: The completed module will be distributed to medical school teaching centers for the instruction of residents and medical students. Home study sets will be loaned to physicians on request.

92. RADIODIAGNOSTIC IRRADIATION IN MEN AND REPRODUCTION

Hirsch, A. F., Hemon, D., Hopital Intercommunal, *40 Ave. de Verdun, 94010 Creteil, France*

The present project is a feasibility study which is preliminary to a research program which aims to obtain relevant information regarding the following questions: 1) What is the statistical distribution of the individual number and type of radiodiagnostic examinations which are performed on men who can potentially father children? 2) What proportion of men who can potentially father children and are exposed to radiodiagnostic examination do actually father children within 3 months following this examination? 3) When radiodiagnostic examination of a man is followed within 3 months by conception, is there any increase in reproductive failures?

93. DIAGNOSTIC ONCOLOGIC RADIOLOGY

Castellino, R., Stanford University, School of Medicine, Dept. of Radiology, *300 Pasteur Dr., Stanford, California*, 94305, United States of America

This is part of a broader project. A summary of this subproject is not available.

II. RADIOTHERAPY METHODS IN CANCER TREATMENT

A. RADIOISOTOPE AND NEUTRON RADIATION THERAPY

94. EXCLUSIVE RADIOTHERAPY WITH CO60 AND CS137 IN CANCER OF THE FLOOR OF THE MOUTH

Bravo Soto, S., Llanos Cifuentes, E., Hospital Regional de Concepcion, Servicio de Radioterapia, *Janequeo 200, Concepcion, Chile*

OBJECTIVE: To determine rates of loco-regional control, complications and survival.

APPROACH: External telecobalt therapy, 5,000 rads over five weeks, to the primary lesion and neck, followed by Cs137 needles overlaid on the primary lesion only. Calculations are performed according to the rules of Paterson and Parker with M.D. Anderson Hospital system for correction of radiographic calculations. In patients with clinical disease of the neck, selective dissection of the tumoral mass that was first palpated six weeks after terminating external therapy. In patients with loco-regional failure, surgical rescue is employed.

95. FEASIBILITY STUDY OF GALLIUM 67 RADIOISOTOPE THERAPY FOR ADVANCED NON-HODGKIN'S LYMPHOMAS

Maruyama, Y., Kim, E. E., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *Leestown Pike, Lexington, Kentucky*, 40507, United States of America

This project is a feasibility study to test the therapeutic administration of Ga67 for advanced Hodgkin's and non-Hodgkin's lymphoma patients. Preliminary calculations have shown that bone marrow toxicity may be a problem in Ga67 administration. One patient with stage IV-B thermal Hodgkin's disease with jaundice and drug refractor disease was treated. The patient showed some regression of tumor by a pancreatic-abdominal scan and liver scan but expired several weeks after treatment before evaluation was complete. No additional patients have been seen in the recent past. The feasibility study needs to be extended but definitely appears real. Effectiveness is still uncertain.

96. SELECTIVE THERMAL NEUTRON CAPTURE THERAPY OF MALIGNANT MELANOMA CELLS USING THEIR SPECIFIC FUNCTIONAL DIFFERENTIATION

Mishima, Y., Kanda, K., Ishida, M., Eguchi, G., Matsuzawa, T., Okamoto, M., Kobe University, School of Medicine, Dept. of Dermatology, *Kobe, Hyogo, Japan*

The objective of this project is to establish the selective thermal neutron capture of malignant melanoma as a prototype of such cancer cells having specific functional differentiation. Melanoma is the cancerous growth of the pigment cells. As malignant transformation occurs, they usually acquire a greater melanin synthesizing ability. Using this cellular property, we developed this treatment after we succeeded with the chemical synthesis of molecular hybrid compounds of 10B atoms and chlorpromazine which binds selectively with indole nuclei of melanin, and also a number of 10B-dopa compounds, molecular hybrids of 10B with substrate for melanin.

Thermal neutrons are absorbed easily by 10B, and this results in the emission of alpha-particles and lithium atoms sharing between them an average total kinetic energy of 2.33 MeV, which is transferred totally to the tissues. Due to the limited travelling range of these charged particles, the primary radiation injury is confined within a distance of 10-14 microns from the point of the activated boron atom. This distance is almost equal to the diameter of individual melanoma cells, therefore our objectives are to selectively accumulate 10B in melanoma cells and to erradicate them with thermal neutron irradiation without serious injury to the surrounding normal tissue.

The significance of this project is not only the cure of melanoma but that this research is readily applicable to many human cancers, such as thyroid and squamous cell carcinoma, which synthesize their specific proteins. The project also offers new methods of investigating radiobiological damage at subcellular levels.

97. FAST NEUTRON THERAPY WITH TAMVEC CYCLOTRON

Fletcher, G. H., Hussey, D. H., Jardine, J. H., Almond, P. R., Olson, M., Burtner, G., Milas, L., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Radiotherapy, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

The primary objective is to determine whether fast neutron therapy is superior to the best current treatment methods in the management of locally advanced malignant tumors. To achieve this goal, prospective randomized clinical trials are under way for a variety of tumor sites. In addition to a continuation of the clinical trial in human cancer, research in physics and radiobiology will be carried out in order to 1) improve neutron treatment techniques and dosage schedules, 2) evaluate population for future clinical trials.

98. AAPM FAST NEUTRON BEAM DOSIMETRY PHYSICS TASK GROUP

Wootton, P., American Assn. of Physicists in Medicine, Division of Medical Radiation Physics, *111 E. Walker Dr., Chicago, Illinois*, 60601, United States of America

The purpose of this application is to: a) Continue the experimental intercomparison of clinically active fast neutron beam radiotherapy projects with regard to fast neutron dosimetry, b) include new clinical projects in this intercomparison as they become active, c) assist the cancer therapy effort in general and the Radiological Physics Center-Houston in its role as the dosimetry quality control arm of RTOG by development of a fast neutron dosimetry protocol based on the best experience and advice currently available. This protocol would then be subject to review by a suitable scientific body.

The field of neutron therapy is in a period of rapid development in facilities of varied backgrounds. This enriches the base of the physics advice and dosimetry methods available but

accentuates the need for a mutually agreeable aproach to the dosimetric basis for national clinical trials of fast neutrons at these centers. This task group will ensure the compatibility of current practices at the various facilities by experimental intercomparison of dosimetry at new facilities as they become active and/or at one established facility so that such experimental exchanges occur at least once per year. Subsequent to acquisition of data and dependent upon opportunity for review and evaluation, meetings will be held to compare the data, plan experimental resolution of differences and develop a protocol of significance to the fast neutron beam therapy trials and to the radiological community, irrespective of the centers' relation to any such proposed national clinical trial.

99. FERMILAB CANCER THERAPY FACILITY

Cohen, L., Awschalom, M., Hendrickson, F., Rosenberg, I., Hrejsa, A., Kaul, R., Mansell, J., Zimmer, D., Bennett, B., Pientak, B., Universities Research Assn. Inc., *2100 Pennsylvania Ave. N.W., Washington, District of Columbia,* 20037, United States of America

The overall objective of the study is to continue a major research program for clinical trials in fast neutron therapy in order to evaluate the effectiveness of neutron therapy relative to other forms of conventional radiation therapy. Since all essential preclinical physical measurements and calibration, radiobiological studies, and pilot studies on patients referred with locally advanced disease have been completed satisfactorily, our objective at this stage is a strictly controlled experiment within a cooperative national protocol to evaluate one modality against another in randomly selected groups of patients. This work will concentrate mainly on subjects eligible for entry into the RTOG protocols: Resectable and Nonresectable Late Stage Cancer of the Head and Neck, Malignant Brain Tumors, Cancer of the Prostate and Bladder, Late Stage Carcinoma of the Cervix, Carcinoma of the Esophagus, Small Cell Carcinoma of the Lung, Carcinoma of the Pancreas, Tumors of Salivary Glands, Radioresistant Adenocarcinomas, Bone and Soft Tissue Sarcomas.

100. FAST NEUTRON BEAM RADIOTHERAPY

Griffin, T. W., Groudine, M. T., Laramore, G. E., Russell, A. H., Tong, D., Wootton, P., Eenmaa, J., University of Washington, School of Medicine, Dept. of Radiology, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington,* 98195, United States of America

The objective of this study is to determine whether fast neutron teletherapy has any advantage over conventional photon teletherapy in the treatment of cancers in humans. The basis for a potential advantage is that hypoxic tumor cells respond better to high LET radiation than conventional photon radiation. Therefore, in those cancers containing even small (1%) components of hypoxic cells, a potential cause of tumor persistence after conventional photon radiation therapy can be reduced or eliminated.

The objective of the physics component is to deliver a controlled quantitated beam of fast neutrons coupled with methods of patient handling alignment and treatment planning such that a valid evaluation of fast neutrons as a treatment modality may be expedited.

The radiation oncology goals are to study tissue tolerance and tumor response to patterns of treatment and initiate cooperative trials with other fast neutron beam therapy centers.

BIBLIOGRAPHIC REFERENCES: Richardson, R.G., Griffin, T.W. and Parker, R.G.: Intramedullary hemangioblastoma of the spinal cord. Cancer 45:49-50, 1980. Tong, D., Griffin, T.W., Laramore, G.E., Kurtz, J.M., Russell, A.H., Groudine, M.T., Herron, T., Blasko, J.C. and Tesh, D.W.: Solitary plasmacytoma of the bone and soft tissues. Radiology 135:195-198, 1980.

101. CLINICAL NEUTRON THERAPY PROGRAM

Antunez, A. R., Cleveland Clinic Hospital, Dept. of Radiation Therapy, *9500 Euclid Ave., Cleveland, Ohio,* 44106, United States of America

The plants developed by the Cleveland Clinic in the first modification of the cyclotron for adaption to clinical use envisioned a second addition. This addition would complete the change of the cyclotron from a physic area into a clinical setting.

102. CLINICAL NEUTRON THERAPY PROGRAM

Griffin, T., University of Washington, School of Medicine, Dept. of Radiology, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington,* 98195, United States of America

OBJECTIVES: To construct a neutron therapy facility with two treatment rooms and necessary ancillary facilities. To procure a cyclotron neutron generator for use in the treatment of cancer patients. To compare results of neutron radiotherapy with the results of the best treatment with x-rays.

103. CLINICAL NEUTRON THERAPY PROGRAM

Goodman, R. L., Fox Chase Cancer Center, *7701 Burholme Ave., Philadelphia, Pennsylvania,* 19111, United States of America

OBJECTIVES: To provide a neutron therapy facility and necessary ancillary facilities to house a DT generator (provided by U.S. Government and University of Pennsylvania). To compare results of neutron radiotherapy with the results of the best treatment with x-rays.

104. CLINICAL NEUTRON THERAPY PROGRAM

Parker, R., University of California, Los Angeles Campus, School of Medicine, Dept. of Radiological Sciences, *2025 Zonal Ave., Los Angeles, California,* 90024, United States of America

OBJECTIVES: To construct a neutron therapy facility with two treatment rooms and necessary ancillary facilities. To procure a cyclotron neutron generator for use in the treatment of cancer patients. To compare results of neutron radiotherapy with the results of the best treatment with x-rays.

B. RADIOTHERAPY WITH PI-MESONS, PROTONS, HELIUM IONS, AND OTHER PARTICLES

105. APPLICATIONS OF PIONS, MUONS, ADVANCED ELECTRONICS, AND COMPUTERS TO MEDICINE

Bradburn, J. N., U.S. Dept. of Energy, Los Alamos Scientific Lab., *P.O. Box 1663, Los Alamos, New Mexico,* 87544, United States of America

The Los Alamos Meson Physics Facility (LAMPF) provides intense beams of mu-mesons and pi-mesons which are, respectively, being evaluated for tissue analysis and cancer radiotherapy. Instrumentation for providing localized heating by means of radiofrequency current fields to selected tissue volumes has also been developed as a means of treating tumors. The technique has been applied to both animals and humans. The experimental data acquired on muonic x-ray spectra from normal and abnormal tisues will be analyzed with the aim of finding signatures linked to the diseased state. Additional experiments are planned to establish sensitivity limits for the determination of elemental composition and the usefulness of the technique in selected practical applications. The hyperthermia research using localized current fields will continue to be applied to spontaneous tumors in animals. Instrumentation already developed will be used in the field to treat the cancer-eye condition in cattle. Finally, preliminary work will begin in collaboration with University of New Mexico personnel to determine the feasibility of using bioelectric potential measurements as a means of detecting human breast cancers.

106. PI-MESON THERAPY OF CANCER

von Essen, C. F., Schweizerisches Institut fur Nuklearforschung, Medical Division, *CH5234 Villigen, Switzerland*

OBJECTIVE: Treatment of patients with cancer by pi-mesons.

APPROACH: A unique 60-channel superconducting spectrometer has been developed for the dynamic therapy of cancer with pi-mesons. In order to fully develop this modality extensive studies in dosimetry, radiation biology, and clinical tumor localization are necessary.

Programs in the following areas are planned to be integrated into an evolving clinical therapy program: 1. Physics research and development: In vivo and in vitro dosimetry, dose calculations and treatment planning, and methodology to improve dose distributions. 2. Radiobiology research: Pion radiobiology in small and large animal systems emphasizing normal tissues. 3. Biology engineering technology: Methods of patient immobilization and target localization: Practical systems for

comfort and rapid treatment, integration of computerized information of diagnostic CT with treatment planning and treatment delivery. 4. Clinical research: Development and standardization of methods to evaluate therapeutic response and morbidity.

PROGRESS: These programs have started and the initial clinical trials are scheduled to begin late 1980.

107. CLINICAL STUDIES OF PION RADIOTHERAPY

Kligerman, M. M., Bush, S., Khan, M. K., Sala, J., Black, W. C., Kelsey, C. A., Smith, A. R., Amols, H., Hilka, R., Bradbury, J., Berardo, P., Paciotti, M., University of New Mexico, School of Medicine, Dept. of Radiology, *University Hill N.E., Albuquerque, New Mexico*, 87131, United States of America

The overall objective of this program is to evaluate the efficacy, potential benefit, and role of negative pi-mesons (pions) in radiotherapy for the management of all types and stages of solid tumors not well managed by current treatment methods or combinations thereof. Phase I-II clinical investigations provide data and experience on the usefulness of pions in treating tumors at several sites, leading to Phase III randomized trials in which pion treatment is compared directly to conventional radiotherapeutic treatment for particular sites. Physics studies develop the pion treatment beam hardware and software, provide basic understanding of pion-beam characteristics, and evolve techniques for measuring dose distribution and volume. Biology studies provide a more definitive understanding of the biologic actions and relative biologic effectiveness of pions, as compared to x-rays, in vivo and in vitro. The linear accelerator at Los Alamos continues to be the only facility in the world that can provide a pion flux adequate for treating clinically relevant volumes. Continued improvement in beam output and treatment technique and the institution of Phase III trials for new sites, should permit a meaningful comparison of the relative effectiveness of pion treatment versus conventional photon treatment.

108. PROTON RADIATION THERAPY RESEARCH

Suit, H. D., Goitein, M., Verhey, L., Koehler, A. M., Schneider, R., Linggood, R. M., Wang, C. C., Shipley, W. U., Gunderson, L., Choi, N. C., Epp, E., Massachusetts General Hospital, Dept. of Radiation Medicine, *32 Fruit St., Boston, Massachusetts*, 02114, United States of America

An exploratory study of fractionated large field proton therapy is proposed. We describe work already performed in the investigation of proton irradiation. This includes investigation of the problems posed by heterogeneity and a description of patients treated by us at the Harvard Cyclotron Laboratory.

The objectives of the study are: (1) to evaluate the potential clinical advantages of proton therapy for selected tumor-normal tissue situations through critical evaluation of comparative treatment plans and treatment of selected patients; (2) to assess the problems posed by tissue heterogeneity through theoretical calculations, use of a CT scanner in a variety of anatomic sites, and confirmatory measurements in proton beams; (3) to make improvements to the treatment facility which will permit routine treatment of a substantial number of patients with one fraction per day and with reliability of dose delivery and beam quality; (4) to measure the proton RBE for small fractionated doses with number of end points; (5) to treat a number of patients with protons in situations in which protons appear to offer an advantage and for which the heterogeneity problem is surmountable; (6) to plan a prospective clinical trial of proton vs. photon therapy; and (7) to design these clinical trials, to the extent feasible, to provide control information for work with pi-meson or heavy ion therapy.

If this program continues to demonstrate significant advantages for the highly localized dose distributions that can be achieved with proton beams, it will offer the potential for improved local control and/or reduction of morbidity for a large class of cancer patients.

BIBLIOGRAPHIC REFERENCES: Suit, H.D. and Goitein, M.: Rationale for use of charged particle and/or fast neutron beams in radiation therapy. In Radiation Biology in Cancer Research. Proceedings of 32nd Annual Symposium on Fundamental Cancer Research, p. 547-565, 1980.

109. TREATMENT OF CANCER WITH HEAVY CHARGED PARTICLES

Castro, J. R., Quivey, J. M., Alpen, E. L., Tobias, C. A., Chen, G. T., Lyman, J. T., Tobias, C. A., Saunders, W., University of California, Berkeley Campus, Lawrence Berkeley Lab., Dept. of Radiology Oncology, *Berkeley, California*, 94720, United States of America

In order to test the potential advantages of improved dose distribution (helium) and increased biological effect (neon, carbon), a clinical trial is being conducted to study the therapeutic application of these heavy charged particles in the treatment of human cancers. Fractionated, large field, spread out Bragg peak charged particle radiotherapy treatment techniques are being continually refined together with improved techniques for assessment and compensation of tissue inhomogeneities utilizing CT scanners to obtain tissue densities in the particle beam paths.

Several pilot protocols with helium have been instituted, leading so far to one randomized trial: helium ion treatment plus 5-FU versus conventional radiation therapy plus 5-FU. We have also instituted Phase I-II pilot studies with heavier ions such as carbon and neon. Our ultimate goal is to test heavy charged particles against the best available therapy in a randomized trial of selected tumors. Existing cooperative study groups such as the Radiation Therapy Oncology Group and the Northern California Oncology Group are being utilized to facilitate these trials, together with the Bay Area Heavy Ion Assessment.

BIBLIOGRAPHIC REFERENCES: Chen, G.T.Y., Singh, R.P., Castro, J.R., Lyman, J.T., and Quivey, J.M. Treatment planning for heavy ion radiotherapy. In: Int. J. of Rad. Onc., Biol., and Phys. Vol 5, 1979. PP 1809-1819.

110. HEAVY PARTICLES IN RADIOTHERAPY - A COMPARATIVE STUDY

Raju, M. R., Tokita, N., Carpenter, S. G., University of California, Central Office, U.S. Dept. of Energy Los Alamos Scientific Lab., Radiobiology & Oncology Section, *P.O. Box 1663, Los Alamos, New Mexico*, 87545, United States of America

Clinical trials using various heavy particles are in progress in the United States: neutrons (multiple locations); protons (Harvard); helium and heavy ions (Berkeley); and negative pions (Los Alamos). During the past three years, our studies have provided physical and radiobiological information not only on evaluating the complementary therapeutic potential for fast neutrons, protons, helium ions, heavy ions, and negative pions but have also helped in developing national plans for particle radiotherapy programs by the Subcommittee on Particle Radiotherapy of the Committee on Radiation Therapy Oncology Group (RTOG).

The proposed project is a continuation of the previous proposal to provide intercomparative and basic radiobiological data for heavy charged particles, particularly for negative pions and heavy ions, and to (1) assist ongoing clinical programs, (2) form a radiobiology background for a comparison of results of various clinical trials, and (3) continue basic high-LET radiobiological studies. Proposed studies include (1) a radiobiological intercomparison between negative pions and heavy ions for single and fractionated doses using acute mouse skin response and intestinal crypt survival; (2) an intercomparison between negative pion beams at Los Alamos, Vancouver, and Zurich for single and fractionated doses using mouse skin response and intestinal crypt survival; (3) RBE determinations for early and late effects in the mouse gut system for negative pions and heavy ions; (4) complementary radiobiology studies to assist ongoing clinical programs with pions and heavy ions; and (5) effects of neutrons from pion stars in pion beams. Basic studies include (1) age-response studies with heavy ions using synchronized Chinese hamster cells (CHO); (2) potentially lethal damage studies of negative pions and heavy ions using plateau-phase CHO cells; (3) combined effects of alpha particles from plutonium and chemotherapeutic drugs on cultured cells; and (4) cell progression delay after alpha-particle irradiation compared to that after X-irradiation.

111. PHASE I-II CLINICAL STUDIES WITH HEAVY CHARGED PARTICLES

Phillips, T. L., University of California, Berkeley Campus, Lawrence Berkeley Lab., *Berkeley, California*, 94720, United States of America

This is part of a broader project. A summary of this subproject is not available.

112. DEVELOPMENT OF A FAST SYSTEM FOR THE DETERMINATION OF BASIC PARAMETERS OF IRRADIATION BEAMS

van de Pool, J. A., Bot, A., Rotterdamsch Radiotherapeutisch Instituut, Dept. of Physics, *Groene Hilledijk 301, Box 5201, 3075 EA Rotterdam, Netherlands*

OBJECTIVE: The dose calculations for radiotherapy patients are based on single irradiation beam dose distributions, measured under stable conditions. For electron accelerators in practice, variations in the dose distributions will occur. To investigate these a fast multipoint sampling system for the irradiation beams will be developed. Thereafter the short-term and long-term variations can be analyzed.

APPROACH: The radiation beams will be sampled with a multiple diode detector. The ratios between the signals from the measuring diodes in relation to the signal of a reference detector will be used in order to analyze the distribution and penetration characteristics of the beams. Such an analysis can be done by simple visual means or via on-line or off-line use of computer systems of different complexities.

113. ELECTRON BEAM TREATMENT PLANNING

Khan, F. M., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Therapeutic Radiology, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

This is part of a broader project. A summary of this subproject is not available.

114. ELECTRON BEAM THERAPY (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

115. FLUORESCENCE ENDOSCOPY AND PHOTORADIATION THERAPY

Balchum, O. J., Profio, A. E., Doiron, D. R., University of Southern California, School of Medicine, Dept. of Medicine, *2025 Zonal Ave., Los Angeles, California*, 90033, United States of America

Fluorescence bronchoscopy was carried out in 5 patients with lung cancer, using a mercury arc light source-bronchoscope system (Chest 76:27-32, 1979), 72 hours after intravenous injection of hematoporphyrin derivatve (2 mg/kg). Fluorescence was noted in 3 of 5. Of the two showing no fluorescence, one was true negative and one was false negative.

Fifteen additional patients had fluorescence bronchoscopy using a laser light source-bronchoscope system (Profio, E.A. et al., Medical Physics, November-December 1979).

Distinct fluorescence was noted in 11 patients with visible endobronchial cancers. Of the 4 with no fluorescence, one was true negative, one false negative; the status of the remaining two is yet to be determined by follow-up and further studies.

Our immediate aim is to demonstrate the diagnostic accuracy of fluorescence bronchoscopy in occult lung cancer (chest X-ray negative, sputum positive for malignant cells), with bronchial tumors too small to be identified reliably or even visualized by conventional white light bronchoscopy. Work in progress is aimed at developing equipment and methods to enhance detecting contrast between fluorescence of even small cancerous bronchial plaques from that of background, and with high accuracy. Pathological specimens resected will be studied to determine extent (area, thickness) and penetration of small bronchial cancers, to understand the stages of occult cancer, and to form a basis for therapy.

116. PHASE II STUDY OF PHOTORADIATION THERAPY

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The primary objective of this program is to evaluate in a Phase II study, photoradiation therapy as a means of local treatment of various malignancies in man. It is planned to determine the scope and limitations of photoradiation therapy and especially to identify situations it may offer a unique advantage over exising therapies as a primary modality, in combination with other modalities or as a treatment for patients who have failed other modalities. Photoradiation therapy involves irradiating hematoporphyrin derivative, which accumulates in malignant tissue, with appropriate laser light in the presence of oxygen. This process generates singlet oxygen, a highly toxic substance.

117. CONTROL OF NEOPLASTIC GROWTH BY PORPHYRIN-SENSITIZED PHOTOCHEMICAL PROCESS

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OBJECTIVE: Inducing the regression and control of tumors at both the experimental and the clinical level by irradiation with visible light (mainly, red light) in the presence of porphyrins. This involves a better understanding of the factors which control the photosensitizing efficiency of porphyrins and of the mechanism which determines the selective uptake of porphyrins by neoplastic tissues.

APPROACH: The following research lines are being pursued: 1. Study of the kinetics of porphyrin distribution in experimental animals as a function of the administration pathway, the injected dose, and the chemical structure. 2. Identification of the sites of porphyrin binding in hepatocytes and in ascitic tumor cells. 3. Determination of the affinity of different porphyrins for various potential ligands (e.g., serum proteins) and for normal and neoplastic cells at different stages of development. 4. Irradiation of hematoporphyrin and some model biological substrates in different media and in the presence of potential inhibitors/enhancers of the photoprocess. 5. Experimental and clinical phototherapy.

PROGRESS: 1. Both i.p.- and i.v.-injected hematoporphyrin accumulates selectively in ascitic tumor cells; the tumor/liver ratio is maximal at about 12 hrs after administration and is higher in the case of i.p. injection. 2. In hepatocytes, about 80% of injected hematoporphyrin is found in the interstitial fluid; the endocellular porphyrin is mainly located in the mitochondria. A key role in the distribution of hematoporphyrin in a I:I molar ratio with a stability constant equal to 10 to the 7th power M to the minus 1st power. 3. The photosensitizing efficiency of hematoporphyrin is controlled both by the aggregation state of the dye and by the polarity of the medium; monomeric hematoporphyrin preferentially induces radical type (electron transfer) photoprocesses, whereas the aggregated porphyrin mainly sensitizes by energy transfer to oxygen with generation of the highly reactive species singlet oxygen.

118. CONTROL OF NEOPLASTIC GROWTH - RADIOTHERAPEUTIC CONTROL

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OBJECTIVE: To check the validity of radiotherapeutic treatment planning, considering the distributions of the possible biological effects. These effects, in the irradiated structures, are deduced from such simple models as N.S.D., T.D.F., etc.

APPROACH: Iso-T.D.F. curves are built either when the dose distribution in the patient is the same in every session, or when it changes. T.D.F. values have been calculated considering the complex treatment as a sum of several simple treatments, of suitable periodicity, and using the T.D.F. addictive property.

119. SEQUENTIAL STEM CELL ASSAY DURING RADIOTHERAPY

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OBJECTIVES: To determine if stem cell assay cloning efficiency varies during the course of radiotherapy.

RESEARCH PLAN: Biopsies will be performed before treatment, at 3000 rads, and at completion of radiotherapy. Routine stem cell assay with determination of cloning efficiency will be performed.

METHODOLOGY: 1 gram samples of tissue taken at initial staging endoscopy, at 3000 rads, and at completion of therapy (if residual tumor is present), submitted for stem cell assay. Histology and cloning efficiency will be compared to clinical response.

FINDINGS TO DATE: Recurrent tumor following radiotherapy has been found in 7 of 12 patients although no sequential analysis has been performed.

120. RADIATION EFFECTS ON THE IMMUNE SYSTEM

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This is part of a broader project. A summary of this subproject is not available.

121. TUMOR THERAPY WITH RADIATION - TREATMENT SCHEMES WITH THE AID OF CELLULAR KINETICS MODELS

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OBJECTIVE: Tumor therapy with high-energy radiation. Proposal of treatment schemes for patients with the aid of cellular kinetics models.

APPROACH: A variety of models describing these factors have been proposed in the literature. The L. Cohen model which we have chosen is not only very demonstrative but, because of its simple mathematics, has the advantage of being a true alternative to the 'Ellis formula' which has been routinely used so far. The parameters contained within this model are to be determined from clinical data for a variety of tumors.

PROGRESS: Since the behavior of a cell population can never be precisely determined, the relevant calculations have to be of a statistical nature. Most of the procedures proposed in the literature to carry out such an analysis have been used without consideration of the specific biological circumstances. The aim of this work is to establish a corresponding statistical approach and to test it for accuracy. The estimated parameters for healthy skin tissue and for various cancerous tissues will allow calculation of optimal treatment schemes. A comparison of these results with calculations based on a number of other models as well as clinical experience should enable us to decide whether application of such calculations has a practical meaning for clinical therapy.

122. IRIDIUM IMPLANTATION BOOST TECHNIQUE (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

123. CARBOGEN BREATHING DURING RADIATION THERAPY (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

124. COMPUTER ANALYSIS OF RADIATION EXPERIENCE

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This is part of a broader project. A summary of this subproject is not available.

C. HYPERTHERMIA ALONE OR AS AN ADJUVANT IN RADIOTHERAPY AND CHEMOTHERAPY

125. LOCAL MICROWAVE HYPERTHERMIA IN TREATMENT OF EXPERIMENTAL AND CLINICAL CANCERS

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Neoplastic cells are more sensitive to elevated temperatures (42-44 degrees C) than normal cells. Controlled intensive hyperthermia (43-45 degrees C) offers a hope for selective destruction of cancer cells, providing that surrounding tissues and immunocompetent cells are protected from elevated temperatures. In addition to the killing of cancer cells by hyperthermia, some other mechanisms, relating probably to the immune system, are triggered, resulting in further destruction heat-inhibited neoplastic cells and inhibition of metastases.

The following subjects will be investigated in the project: cell membrane permeability and ionic transport in normal and neoplastic cell cultures heated to 41 and 43 degrees C; effect of elevated temperatures (40 and 43 degrees C) on function of isolated lymphocytes and macrophages in vitro; effect of whole body and local microwave hyperthermia on cell mediated immune reactions in normal and tumor bearing animals; construction of microwave systems (2450 MHz, 434 MHz, 27 MHz) for local tumor heating in small (mice, rats) and large (dogs, piglets) laboratory animals. Combination of local microwave hyperthermia and immunotherapy (general and intratumoral) with bacterial products (Clostridium oncolyticum, isolated cell wall fractions from Propionibacterium granulosum, also known as Corynebacterium acnes, KP-40); preliminary clinical trials with local microwave hyperthermia combined with immunotherapy.

126. MICROWAVE-INDUCED HYPERTHERMIA FOR DEEP-SEATED TUMORS

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This project proposes to use an invasive microwave irradiation system to achieve local hyperthermia for the treatment of deep-seated cancers. Microwaves in the GHz range are characterized by short energy absorption lengths in living tissue. It is proposed that this characteristic will be exploited and the energy will be delivered directly to the tumor site through transmission lines and antenna structures which have been developed in our laboratory. Antenna probes with diameters less than 1 mm will be employed. Thus, implantation can be performed with minimal disturbance to the surrounding tissue, and many of the problems associated with the delivery of heat to deep-seated tumors will be circumvented.

The objectives of this study are: (1) To further develop an invasive system for heating deep-seated tumors and to adapt the system for percutaneous insertion and surgical implantation so as to produce appropriate hyperthermia in difficult to heat, deep-seated tumors in humans; (2) to predict theoretically, and to measure experimentally, the heat distributions produced by the improved system in tissue phantoms, tumors and normal tissues of animals and humans; (3) to evaluate the therapeutic efficacy of the proposed system by studying the effect of the induced hyperthermia, alone, and in combination with ionizing radiation and chemotherapy on animal tumors, and in pilot clinical studies; and (4) to examine the effect of local hyperthermia on blood flow and the uptake of chemotherapeutic drugs in tumors and in normal tissues.

These tumors will include transplantable mouse mammary adenocarcinoma (MTG-B), chemically induced tumors in the rat, and spontaneous brain tumors in dogs. The effects of the treatment on tumor cell viability will be assessed using the TD50 and tumor latency assays as well as histological evaluation. Tumor growth, TCD50 and host lifespan will also be studied as indicators of therapeutic effectiveness, and normal tissue response will be carefully observed in heated animals. Clinical tumors will include brain tumors and other tumors such as pancreas and prostate cancer.

127. CONTROL OF TUMOR GROWTH - TUMOR CELL SENSITIVITY TO HYPERTHERMIA

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OBJECTIVE: Identification of enzymatic systems involved in the biochemical damage imputable to hyperthermic treatment (42-43 degrees C).

APPROACH: Some aspects of tumor cell metabolism after hyperthermic treatment as such, or in addition to ultraviolet and/or ionizing radiation will be studied. Incorporation of radioactive uridine or thymidine into nucleic acids or oxygen

uptake will be performed in order to test heat sensitivity of normal and tumor cells. Cell suspensions of experimental tumour or untreated cells will be used. The modification of human melanoma metabolism in vivo after hyperthermic treatment will be studied in human patients.

PROGRESS: An inverse relationship between the extent of cellular damage brought about by intracellular formation of superoxide anion, and the efficiency of the glutathione mediated hydrogen peroxide detoxifying system was observed. Ehrlich ascites tumor cells as examples of low content and Yoshida ascites tumor cells as examples of high content of these enzyme systems were used. These results shall be reinvestigated under hyperthermic conditions in order to ascertain a possible involvement of oxygen radicals in the biochemical mechanism of hyperthermia in tumor cells (Lin et al., Rad. Res. 77, 501, 1979).

128. LOCAL HYPERTHERMIC CANCER THERAPY

Storm, F. K., Morton, D. L., Elliott, R. S., Harrison, W. H., Haskell, C., Parker, R., Weisenburger, T., Golub, S. H., University of California, Los Angeles Campus, School of Medicine, Dept. of Surgery, *2025 Zonal Ave., Los Angeles, California*, 90024, United States of America

One of every four Americans living today has or will develop cancer, and one-third will be cured by present modes of therapy. The frequent failure rate of surgery, radiotherapy, chemotherapy and immunotherapy indicates that other forms of therapy are needed. Investigation of other investigators and our preliminary trials in animals and man tend to support the hypothesis of selective thermal-sensitivity of tumors, and suggest that hyperthermia therapy may be of benefit in treating human cancer.

Lack of prior instrumentation capable of providing safe, effective, deep hyperthermia has not allowed research in man to significantly progress beyond more superficial cancers. We have developed specialized shortwave radiofrequency devices which allow effective hyperthermia to any depth without injury to normal tissue.

The objectives of this proposal are to further test the hypothesis of selective thermosensitivity of human tumors and evaluate the potential role of hyperthermia in the local treatment of solid cancers, both as a single modality and in combination with radiotherapy or chemotherapy.

Our newly developed equipment will be further evaluated for its capacity to provide superficial and deep hyperthermia to normal organs and tumors of different type, size and location. The tumoricidal effect of various temperatures and treatment schedules will be investigated and standardized. The effect and potential benefit of combined radiotherapy and chemotherapy will be explored under standardized conditions. An associated immune-mediated response will be sought by evaluation of non-treated tumors, and monitoring immune-related parameters.

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129. WHOLE BODY- AND LOCAL HYPERTHERMIA

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OBJECTIVE: Hyperthermic treatment of human tumors.

APPROACH: Whole body hyperthermia (Siemens Cabin) plus microwave local hyperthermia; also tumor pH measurements.

PROGRESS: Thirty-three whole body treatments have been performed on 17 patients, in addition to localized X-ray treatment. Some 40 patients have received a combination of X-ray treatment and local microwave heating. Some 40 different tumor-pH measurements have been performed, about half of them on mammary carcinomata. Seven determinations of tumor pH during whole body hyperthermia have been performed. The data indicate that further evaluation is required.

130. HYPERTHERMIA (PHANTOM MODELS, PIGS, RABBITS, HUMANS)

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This is part of a broader project. A summary of this subproject is not available.

131. LOCALIZED ELECTRO-MAGNETIC HEATING

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This is part of a broader project. A summary of this subproject is not available.

132. WHOLE BODY HYPERTHERMIA AS AN ADJUVANT TO SYSTEMIC CHEMOTHERAPY IN PATIENTS WITH ADVANCED MALIGNANCIES

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Ten patients (3 with malanoma, 3 with colon cancer, 2 with sarcomas, 1 with lymphoma, and 1 with acute leukemia) with advanced cancers unresponsive to standard therapy were given a total of 25 heat treatments administered by extracorporally heating their blood. Peak temperatures achieved were between 42 and 42.4 degrees C and maintained for 2-3 hours. Cisplatinum 60 mg/m2 IV or BCNU 20 mg/m2 IV was administered just as peak temperature was reached. Thus far we have seen objective partial response in 6 of nine evaluable (67 percent) patients. The most gratifying response occured in the patient with lymphoma whose leukemic phase marrow was cleared by treatment. Toxicity has been considerable. Electrolytes, fluid and cardiac problems are similar in degree to those reported by others utilizing whole body hyperthermia but the consumption of coagulation factors, especially platelets, has been more extreme (nadir counts in all patients less than 15,000). One patient died as a result of therapy. Autopsy revealed that this patient bled into extensive necrotic pulmonary metastasis from a Ewing's sarcoma.

133. EFFECTS OF HEAT AND RADIATION ON NEOPLASMS - OPTIMAL FRACTIONATION

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This study represents one portion of a major program in our laboratory whose objectives are to 1) understand the mechanisms of action involved in the selective radio- and chemosensitization of neoplastic tissues and cells by hyperthermia, and 2) utilize this knowledge in the treatment of cancer. To this end animal studies, in vitro cellular studies, and clinical studies are currently under way. The objective of the present proposal is to compare the responses of neoplastic and normal tissues of the mouse to local tumor hyperthermia (LTH) and radiation to evaluate the time-dose relationship of combined radiation and hyperthermia to the therapeutic ratio. It is proposed that these studies be carried out using a fibrosarcoma grown in BALB/c mice. Comparisons of the time-dose response of the tumor vs. normal tissues will help establish treatment parameters which will optimize the therapeutic ratio.

134. ANESTHETICS AS RADIATION AND/OR HYPERTHERMIA ADJUNCTS

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Results from this laboratory indicate that certain clinically used pharmacological agents such as some local anesthetics, barbiturates, tranquillizers, etc. can radiosensitize and inactivate hypoxic cells, radioprotect oxic cells, and potentiate the hyperthermic killing of cells. One aspect of this research will be to elucidate the basic mechanism(s) whereby such effects are exerted. We will continue to screen rationally and, to a certain extent, synthesize derivatives of anesthetics or related compounds which appear to be promising so that the structure-activity relationship can be established. Parameters to be correlated with radiation modifying capacity will include electron affinity, radical scavenging activity, solubility, acid/base equilib-

ria, partition coefficient, cytotoxicity and ability to alter cellular oxygen consumption. The efficacy of some of these compounds relative to the more conventional hypoxic radiosensitizers, radioprotectors or hypoxic cytotoxic agents currently under investigation in many other laboratories will also be compared. Lastly, we will also investigate to see if the well-known synergism between radiation and hyperthermia can be additionally augmented by the application of selected anesthetics or related compounds.

We anticipate that these studies might (1) provide impetus for the continual search for related compounds that might possess a radiation and/or hyperthermia modifying capacity as well as pharmacological properties required of an ideal adjunct for the radiotherapy of human tumors, and (2) help to identify the basic mechanisms and sites of damage for cellular inactivation by hyperthermia and radiation, as well as for radiosensitization by heat.

135. MICROWAVE DIATHERMY AND RADIOTHERAPY OF MALIGNANT TUMORS

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The 50 patients treated to date have had squamous cell carcinoma, adenocarcinoma, malignant melanoma, plasmacytoma, liposarcoma, epithelioid sarcoma, and undifferentiated carcinoma. After more than 500 hyperthermia sessions, we find: (1) local hyperthermia with microwave alone or in combination with ionizing radiation can be used with excellent normal tissue tolerance provided local tissue temperatures are carefully monitored and controlled; (2) a significantly higher level of preferential heat induction into tumor tissue as compared to surrounding normal tissues; (3) repeated hyperthermia at 42-43.5 degrees C for 45 minutes per session immediately following photon irradiation yields a favorable therapeutic ratio. At 22 months maximum follow-up, no normal tissue injury is clinically apparent. No patient withdrew due to heat related discomfort, and the hyperthermia sessions were well tolerated. Local hyperthermia in combination with radiotherapy offers the possibility of substantial impact on clinical cancer therapy, whether of curative or palliative intent. The main objective of continuing this protocol is to gather data on the responses of tumor and normal tissues after combining localized hyperthermia with conventional radiotherapy. This will eventually lead to full clinical trials with an adequate electromagnetic hyperthermia system (i.e., for tumors in deep tissues).

136. HEAT AND RADIATION IN CANCER THERAPY

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The objective of this program is to determine the efficacy of hyperthermia, either used alone or as an adjuvant to radiation, as a therapeutic modality in the treatment of human malignancies. The proposed research involves a multidisciplinary effort, including biological, physical, and clinical scientists. Specific projects within this program will study a broad range of the biological effects of hyperthermia, spanning molecular and biochemical, cellular and organized tissue systems, including both tumor and normal tissues. Other projects will focus on techniques to produce elevated temperature distributions in biological systems and then measure these temperature patterns. The experimental studies will provide the biological and physical information required for the initial studies employing hyperthermia in the treatment of human neoplasms. The basic science projects also have the goal of further developing the rationale for and the understanding of the clinical potential of hyperthermia. The clinical projects of this program will initiate studies to explore the clinical efficacy of hyperthermia, both as a local and systemic modality, combined with radiation.

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137. MICROWAVE HYPERTHERMIA AND RADIATION IN CLINICAL ONCOLOGY

Mantik, D. W., Loma Linda University, School of Medicine, Dept. of Radiation Oncology, *Loma Linda, California,* 92350, United States of America

OBJECTIVE: Enhanced response of human cancers.

APPROACH: Use of BSD-1000 Hyperthermic Unit in conjunction with radiation therapy for advanced or recurrent cancers not easily amenable to standard therapy.

PROGRESS: Several patients have already been treated at Loma Linda, as reported in the Thermal Journal, volume 2, No. 1, published by BSD Corporation, Salt Lake City, Utah.

138. INTERACTION OF HYPERTHERMIA, RADIATION AND DRUGS IN VITRO (HAMSTERS, HUMANS)

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This is part of a broader project. A summary of this subproject is not available.

139. VHF AND MICROWAVE HYPERTHERMIA AND IRRADIATION (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

140. EFFECTS OF LOCALIZED HEAT AND IRRADIATION ON MALIGNANCIES

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This is part of a broader project. A summary of this subproject is not available.

141. CLINICAL HYPERTHERMIA AS AN ADJUVANT IN RADIATION THERAPY (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

142. RADIATION-HYPERGLYCEMIA/HYPERTHERMIA INTERACTION

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This is part of a broader project. A summary of this subproject is not available.

D. MULTIPLE THERAPY MODALITY

1. RADIOTHERAPY AND CHEMOTHERAPY

143. EFFECTS OF CNS TREATMENT ON INTELLECTUAL FUNCTIONING OF CHILDREN WITH LEUKEMIA

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The effects of CNS treatment (cranial irradiation and intrathecal chemotherapy) on the cognitive and perceptual functioning of children with leukemia are investigated. One study compared a group of leukemic children in remission with a matched group of sibs. Comparisons were based on results from a battery of psychological tests (Wechsler, Bender-Gestalt and Graham-Kendall) administered to the children. These groups are followed-up 12-15 months after the initial assessment. A sample of leukemia patients who have not received CNS treatment and their sibs and a sample of cystic fibrosis patients and

their sibs are also being assessed using these procedures to control for effects other than CNS treatment. A second study deals with another sample studied prospectively. In this instance children in remission from leukemia are evaluated on the same battery of psychological tests as in the first study. They are tested just prior to prophylactic CNS treatment and are re-evaluated one year later to determine if any possible brain changes brought on by the CNS treatment have resulted in learning disabilities and diminished intellectual functioning. The healthy siblings of the leukemics receiving CNS treatment, who are being studied retrospectively, will be used as a control group to check testing effects.

144. LATE EFFECTS OF CANCER TREATMENT IN CHILDREN INCLUDING SECOND MALIGNANT NEOPLASMS - CHILDREN'S INTERNATIONAL CANCER INVENTORY

Meadows, A. T., Banfi, A. D., Voute, P. A., Baum, E. S., D'Angio, G. J., Evans, A. E., Jenkin, R. D., Morris Jones, P. H., Newton, W. A., Siegel, S., Green, D., University of Pennsylvania, Childrens Hospital of Philadelphia, *34th St. & Civic Ctr. Blvd., Philadelphia, Pennsylvania*, 19104, United States of America

As treatment for childhood cancer was becoming more successful and survivors were increasing, an interest developed in studying these children for late effects to organ systems of radiation and chemotherapy. Also of interest was the rate of second tumors in these survivors, whether treatment-related or not. Begun in 1972 at three pilot institutions, the study has been expanded to include children with cancer at 13 institutions, particularly with reference to: (1) the relationship of second malignant neoplasms (SMN) to therapy and other aetiological factors, (2) the incidence of SMN, (3) histopathology of SMN (4) survival of patients with SMN, (5) unusual tumors in children with cancer, (6) congenital anomalies in patients, (7) data regarding siblings and other family members for cancer and congenital defects, and (8) other deleterious sequelae encountered in patients cured of cancer in childhood. All studies are now active, including a case-control study of the 200 SMN in our registry to 1979.

145. COMPARISON IN HODGKIN'S DISEASE OF CHEMOTHERAPY ALONE VS THE COMBINATION OF CHEMOTHERAPY PLUS RADIOTHERAPY IN THE INVOLVED FIELD

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OBJECTIVES: I. Evaluate in patients without previous treatment, according to clinical stage, different therapeutic modalities, comparing combination chemotherapy to radiotherapy plus combination chemotherapy. II. Evaluate the usefulness of lower doses and radiation directed to involved areas exclusively with the aim of reducing dose and radiation areas. III. Use as combination chemotherapy the combination CVPP which has shown its usefulness and therapeutic response similar to more aggressive therapeutic combinations such as COPP, MOPP.

METHODS: Induction: Arm I: Radiotherapy 3000 rads to involved lymphatic areas and after 6 cycles of CVPP (CTX 600 mg/m2 i.v. day 1; VCR 6 mg/m2 i.v. day 1; PCB 100 mg/m2 po day 1 to 14; PRED 40 mg/m2 po day 1 to 14). Arm II: Three cycles of CVPP as in Arm I and afterwards radiotherapy 3000 rads to the previously involved lymphatic areas followed by 3 cycles of CVPP. Arm III: Six cycles of CVPP only. Maintenance: Patients will be randomized between: Arm I: Continue maintenance course of CVPP every 2 months the first year and every 4 months the second year, or Arm II: No further treatment, or Arm III: Levamisole.

PROGRESS REPORT: Up to June 1978, 92 patients entered onto the study, of whom 24 are still in the induction phase and 68 have completed the induction. Of these patients, 57 (87%) achieved complete remission.

146. HODGKIN'S DISEASE - COMBINATION THERAPY FOR RELAPSE FOLLOWING RADICAL RADIOTHERAPY

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The results of mustine, vinblastine, procarbazine, prednisolone (MVPP) combination chemotherapy for relapsed Hodgkin's disease in 33 patients who were treated initially by definitive radiotherapy are analyzed. Twenty-three of 27 who received chemotherapy at first relapse achieved complete remission; 20 of these remained at remission at periods of 13-96 months (median 53 months) from treatment. Six patients were retreated by irradiation at first recurrence and all suffered further relapse within 14 months. Only three of this group achieved complete remission with subsequent chemotherapy. The results of radiotherapy for early stage Hodgkin's disease are improving now that certain presentations are recognized to be associated with high risk for relapse when treated by irradiation alone. The high rate of complete remission obtained with MVPP in patients with recurrence after radiotherapy suggests that chemotherapy may reasonably be withheld in the initial management of localized disease, thus reducing the risk of iatrogenic complications associated with combination therapy.

147. SECOND PRIMARY MALIGNANCIES FOLLOWING RADIOTHERAPY OR CHEMOTHERAPY OR BOTH FOR HODGKIN'S DISEASE

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The objective is to determine whether intensive radiotherapy or chemotherapy or their combination used in management of Hodgkin's disease is the cause of an increased incidence of secondary primary malignancies within 20 years after exposure. If an increase is found, it is desired to identify the details of the exposure responsible, the time relationships of the effect, and the spectrum of types of second malignancy. Approximately 2,000 patients with Hodgkin's disease treated in 1960 or later will be enrolled and followed for incidence of second malignancies. Patients will be ascertained through the collaboration of approximately 10 clinical centres in the United States and Canada. The study is planned as an independent test of the hypothesis derived from observations made at the National Cancer Institute, U.S.A, of an increased incidence of the total group of all malignancies. This increase is approximately 3-fold in patients given extensive chemotherapy or intensive radiotherapy and may be severalfold greater in patients given intensive courses of either therapy after relapse following an intensive course of the other therapy.

148. RADIOTHERAPY, CHEMOTHERAPY OR COMBINED MODALITY TREATMENT FOR EARLY HODGKIN'S DISEASE

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Eighteen patients with stage II-IIIA1 Hodgkin's disease have been randomly allocated to receive either radiotherapy, MOPP chemotherapy, or the combination of the two modalities for treatment. The study is designed to determine the best therapy for patients with early stage Hodgkin's disease. This study is an ongoing one and represents a long-term commitment the objective of which is to precisely define optimal treatment for this group of young individuals suffering from a malignant disease. In addition, the study asks whether the treatment of Hodgkin's disease might be simplified from the standpoint of expense, morbidity, and comfort by minimizing treatment for subgroups of patients who require less therapy. The long-term consequences of effective therapy will be evaluated in this study over a period of years.

149. RADIOTHERAPY PLUS CHEMOTHERAPY VS. CHEMOTHERAPY ALONE IN HODGKIN'S DISEASE

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PROJECT OBJECTIVES: 1. To find ways of improving therapy for those patients with Hodgkin's disease and unfavorable prognosis. 2. To determine if the combination of chemo-

therapy and irradiation will result in improved response and duration of remission.

PLAN: Patients will be randomized to receive either involved field radiotherapy followed by 6 courses of chemotherapy with BCNU, Cyclophosphamide, Vinblastine, Procarbazine and prednisone or they will receive the same chemotherapy without irradiation. Those patients receiving chemotherapy alone will be reevaluated after three courses and if they have not had a good response, they then will receive involved field radiotherapy.

METHODOLOGY: All previously untreated patients with Stage I, II or III Hodgkin's disease of mixed cellularity or lymphocyte depleted histology, and/or patients over the age of 40 will be eligible for this study.

RESULTS TO DATE: There have been no eligible patients admitted to the VAH.

150. CANCER RISK AFTER IRRADIATION AND/OR CHEMOTHERAPY

Schottenfeld, D., Tan, C. T., Hajdu, S. I., Mohan, R., Reid, A. M., Brody, R. S., Memorial Sloan Kettering Cancer Center, Dept. of Medicine, *1275 York Ave., New York, New York,* 10021, United States of America

The primary objective is to determine whether Hodgkin's disease patients are at increased risk of developing multiple primaries following varying doses and/or ordered sequences of radiation therapy and chemotherapy (given singly or in combined regimes). Histopathological classification of Hodgkin's disease and the extent of disease at first treatment will be studied in relation to the patterns of second primary cancer occurrence by organ site and histopathology. Quantitative estimation of radiation exposure will consider the total dose of radiation delivered, the energy used, the volume of tissue irradiated and the fractionation pattern of the treatment. Multiple entry and exit life tables will be used to characterize temporal patterns of exposure to different treatments, either alone or in combination. Patients will be withdrawn as transfers (not losses) from one treatment classification to another according to interval following first treatment. Internal historical cohorts of patients having received different doses and combinations of therapy will be identified and followed longitudinally to contrast their subsequent multiple primary cancer experience. Risk of new primary cancer among 1,500 Hodgkin's disease patients who have been intensively treated with potentially carcinogenic drugs, such as alkylating agents and steroid hormones, should identify carcinogenic doses or treatment combinations.

151. CHEMOTHERAPY AND LOW DOSE RADIOTHERAPY IN HODGKIN'S DISEASE (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

152. WHOLE-BODY RADIATION VERSUS CHEMORADIOTHERAPY IN PULSES FOR NON-HODGKIN'S LYMPHOMA III-IV

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OBJECTIVE: To determine if differences exist between results of treatment of non-Hodgkin's lymphoma with whole-body irradiation (WBI) and with simultaneous chemotherapy and WBI in intermittent pulses. To determine if there are differences between clinical and/or hematological tolerance to both methods.

APPROACH: Patients are stratified according to histologic variety of non-Hodgkin's lymphoma and then randomized into two treatment groups. Group A is treated with WBI whereas Group B receives chemoradiotherapy in pulses. WBI is applied in a total dose of 150 rads to the midplane in 10 fractions administered in 12 days. The combined treatment consists of procarbazine 100mg/m2/day for 10 days p.o., vincristine 1.5 mg/m2/ iv on days 5 and 10, and prednisone 40 mg/m2/day for 10 days p.o. On days 5 and 10 an application of 10 rads to the whole body plus a boost of 200 rads to the most compromised area. The pulses of chemoradiotherapy are administered every 28 days for a total of 8 pulses. (Translated)

153. TREATMENT OF LOCALIZED MALIGNANT LYMPHOCYTIC AND HISTIOCYTIC LYMPHOMAS WITH COMBINATION OF DRUGS AND IRRADIATION

Neiman, P., Sullivan, K. M., Fred Hutchinson Cancer Research Center, Division of Oncology, *1124 Columbia St., Seattle, Washington,* 98104, United States of America

This project studies the utility of combined modality therapy in localized non-Hodgkin's lymphoma. Patients with Stage I or II histiocytic or diffuse poorly differentiated lymphocytic lymphoma as well as patients with Stage II nodular lymphocytic or mixed lymphomas are selected for induction treatment with local radiation therapy and chemotherapy (Cytoxan, vincristine and prednisone). Consolidation is given with 4 courses of monthly CHOPP (Cytoxan, Adriamycin, vincristine, prednisone and procarbazine) followed by 150 rad total body irradiation. Remission induction, toxicities and relapse rates are monitored. Treatment is delivered on an outpatient basis, often by practicing physicians in the community.

154. POSTOPERATIVE ADJUVANT COMBINED RADIOTHERAPY-CHEMOTHERAPY TREATMENT IN LOCALIZED OSTEOGENIC SARCOMA

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OBJECTIVES: a) To increase the percentage of cures or the disease-free time. b) To determine the duration of the disease-free time. c) To evaluate toxicity of the treatment schedule. d) To evaluate the differences between amputation and bone replacement.

METHODS: a) Patient selection. b) Previous treatment studies. c) Treatment: Surgery: bone replacement or amputation. Cobalt therapy: 15-20 days after surgery; both lung fields, 175 rads daily for 10 days, without lung correction. Chemotherapy: 7-10 days after radiotherapy: adriamycin (50 mg/m2 iv); cyclophosphamide (600 mg/m2 iv) and vincristine (1.4 mg/m2 iv), every 28-30 days, for the first six months. Cyclophosphamide (400 mg/m2 iv) days 1, 2, and 3, every 28-30 days for another six months. d) Monthly controls during the treatment. e) Dose modification according to the toxicity. f) Completion of follow-up sheets.

155. EWING'S SARCOMA TREATMENT WITH HIGH DOSE IRRADIATION AND ADJUVANT CHEMOTHERAPY

Malpas, J. S., Graham Pole, J. R., Pritchard, J., Sandland, M. R., Barrett, A., Bloom, H. J., McElwain, T. J., Imperial Cancer Research Fund, Medical Oncology Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Twenty-one patients with pathologically proven Ewing's sarcoma but without overt metastases at diagnosis were treated with radiotherapy and a combination of four cytotoxic drugs. Fourteen are free from disease a median of 36 months after diagnosis. Comparison with an historical control group of 19 patients treated with surgery or radiotherapy but without initial chemotherapy shows a significant improvement in survival. Seventeen of the control group have died. The regimen was moderately toxic but there were no treatment-related deaths. The longest period of follow-up is now seven years. There have been no second tumors.

156. RADIOTHERAPY WITH RAZOXANE FOR CHONDROSARCOMAS

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Chondrosarcomas are, by common consent, radio- and chemo-resistant. A radiosensitizer ought to be able to improve the dismal results obtained by radiotherapy in this malignancy. Razoxane has shown radiosensitizing properties in vitro, in vivo and in the clinic, particularly in soft tissue sarcomas. It has therefore been examined as a radiosensitizer in the treatment of chondrosarcomas.

Ten patients with 14 chondrosarcomas (three patients had multiple metastases) were treated with doses of radiation ranging from 1950 rads in 13 fractions over 17 days to 6000 rads in 30 fractions over 52 days. On radiation treatment days all patients received 125 mg razoxane twice daily.

Seven sites in five patients showed varying degrees of responses. There were three complete and two partial regressions but even in those five sites where the tumors showed no change in size there was either radiological or histological evidence of extensive radiation-induced calcification or necrosis. Only one patient was completely resistant to the combined treatment and had undiminished progression.

There was no evidence of either early or late radiation reactions in normal tissues, nor was it necessary to interrupt radiotherapy in any of the patients because of additional hematological or other toxicity.

The present results indicate that chondrosarcomas can become sensitive to radiation when treated by the combination of radiotherapy and razoxane. The mechanism of this enhanced radiation effect is not yet clear but in vitro studies indicate that razoxane stimulates DNA synthesis; it may be that this DNA is either fragile or presents a greater target area with the result that cells that have been exposed to razoxane may be unable to undergo repair or may accumulate damage caused by radiation. Since chondrosarcomas are rare, a multi-center (or multi-national) trial might be set up to examine the value of razoxane/radio therapy combination in this tumor.

157. COMBINED RADIO- AND CHEMOTHERAPY - OSTEOGENIC SARCOMAS

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This is part of a broader project. A summary of this subproject is not available.

158. COMBINED CCNU AND RADIOTHERAPY IN MALIGNANT BRAIN TUMORS

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OBJECTIVE: To study: 1) The results of whole brain irradiation versus local tumor area irradiation in malignant brain tumors and (2) the results of combined CCNU and radiotherapy versus radiotherapy alone in malignant brain tumors.

APPROACH: Participating institutions are Tampere and Jyvaskyla Central Hospitals. Adult patients with malignant brain tumor will be randomized into four different treatment groups: 1) Whole brain radiotherapy with CCNU; 2) whole brain radiotherapy without CCNU; 3) local tumor area radiotherapy with CCNU; 4) local tumor area radiotherapy without CCNU. The results will be evaluated in terms of recurrent free period and survival time.

159. COMBINED CHEMO- AND RADIOTHERAPY OF BRAIN TUMORS

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This is part of a broader project. A summary of this subproject is not available.

160. MALIGNANT GLIOMA RADIOTHERAPY PLUS BCNU CHEMOTHERAPY COMPARED TO RADIOSENSITIZED RADIOTHERAPY PLUS BCNU CHEMOTHERAPY

Cox, J. D., Byhardt, R. W., Kun, L. E., Greenberg, M., Komaki, R., Gunn, W., Rangala, N., Wilson, J. F., Holoye, P. Y., Larson, S. J., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *5000 W. National Ave., Wood, Wisconsin*, 53193, United States of America

PROJECT OBJECTVES: To establish the relapse-free mean survival time and overall survival in patients treated with misonidazole radiosensitized irradiation combined with BCNU chemotherapy compared with standard irradiation combined with BCNU chemotherapy.

PLAN: To determine the incidence of any increased toxicities or brain complications when misonidazole radiosensitized irradiation is combined with BCNU chemotherapy.

METHOD: Patients will receive BCNU 80 mg/M2 I.V. on days 3, 4, and 5 of the first week of radiotherapy, then BCNU 80 mg/M2 I.V. x 3 days q. 8 weeks beginning day 64. Radiotherapy will be given as follows: 200 rad/day x 5 days a week x 6 weeks (6000 rad to the whole brain). Radiosensitized radiotherapy plus chemotherapy: Patients will receive oral misonidazole (2.5 grams per M2) four hours prior to a 400 rad fraction of whole brain irradiation each Monday for 6 consecutive weeks. BCNU 80 mg/M2 I.V. will be given on days 3, 4, and 5 of the first week of radiotherapy, then BCNU 80mg/M2 I.V. x 3 days q. 8 weeks beginning day 64. During that time irradiation without radiosensitization will continue with 150 rad each Tuesday, Thursday and Friday of these 6 consecutive weeks. Thereafter the brain will be treated with an additional 180 rad in 5 fractions over one week with radiosensitization.

RESULTS REACHED TO DATE: None. One patient has been treated with radiosensitized radiotherapy plus BCNU chemotherapy with no adverse reactions or complications.

PUBLICATIONS: None. Protocol is still currently active.

161. BCNU, MEDROL, PROCARBAZINE AND RADIOTHERAPY FOR BRAIN GLIOMAS (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

162. CRANIAL VAULT RADIOTHERAPY AND COMBINATION INTRATHECAL CHEMOTHERAPY IN THE TREATMENT OF MENINGEAL CARCINOMATOSIS

Bunn, P. A., Minna, J. D., Cohen, M. H., Ihde, D. C., Matthews, M. J., Myers, C., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *50 Irving St. N.W., Washington, District of Columbia*, 20422, United States of America

The specific aim of this study is to determine whether addition of the alkylating agent, thio-TEPA, to the standard regimen of craniospinal radiotherapy, IT-MTX, and dexamethasone results in improved survival of patients with meningeal carcinomatosis. Diffuse involvement of the leptomeninges with tumor occurs commonly in patients with metastatic breast carcinoma, metastatic lung cancer, melanoma and histiocytic lymphoma. Co-existing CNS mass lesions are seen in 25%-75% of patients with meningeal carcinomatosis. The prognosis of patients with meningeal carcinomatosis is poor. In recent series, the median survival for patients with a variety of primary tumors was less than 6 weeks from the time of diagnosis of the meningeal involvement. Currently used treatment modalities involve the use of cranial (or craniospinal) radiotherapy, intrathecal methotrexate, or combinations of the two. Sixteen patients with breast cancer and meningeal carcinomatosis have recently been treated at the Memorial Hospital. One out of four responded to IT-MTX alone; three out of eight responded to craniospinal radiation alone; and three out of four responded to a combination of craniospinal radiotherapy and intrathecal methotrexate. Systemic chemotherapy, even with drugs that cross the blood-brain barrier, do not appear to be effective.

163. COMBINED EFFECTS OF RADIATION AND CYTOTOXIC DRUGS ON THE RADIATION TOLERANCE OF THE CENTRAL NERVOUS SYSTEM

Hopewell, J. W., Karbal, A., University of Oxford, Research Inst., *c/o Churchill Hospital, Oxford, England, United Kingdom*

OBJECTIVE: Chemotherapeutic agents, in particular methotrexate, are currently being used in conjunction with brain irradiation as part of the prophylactic treatment of children with leukemia. It is proposed to examine the possible effects of various drug combinations on the radiation tolerance of the central nervous system.

APPROACH: It is proposed to investigate the mechanisms responsible for the development of damage in the brain and spinal cord in experimental animals. Effects will be evaluated by the quantitative assessment of cellular changes in histological material obtained by the serial killing of treated animals. The importance of field size will be investigated.

Modifications in normal tissue and tolerance produced by radiation of the spinal cord in combination with various dose levels of intrathecal methotrexate and other drugs will be determined by establishing the proportion of animals developing paralysis after 6 months. Iso-effect doses will be compared to determine the relative changes in cord tolerance.

In the brain, radiation depletion of the cells in the subependymal plate region will be used as a measure of radiation effects. Modifications in this response, produced by drug combinations, will be evaluated.

164. POSTOPERATIVE PROTRACTED COMBINATION CHEMOTHERAPY VERSUS POSTOPERATIVE RADIOTHERAPY IN AXILLARY POSITIVE LYMPH NODES IN EARLY BREAST CANCER

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OBJECTIVE: To assess long-term results of these two postoperative modalities of treatment in early cancers of breast and to define their value in prevention of local or systematic recurrence and to assess survival and cure rate.

APPROACH: All patients with clinically early cancers of the breast are operated on by standard radical mastectomy. Careful axillary dissection is carried out. The palpable nodes are marked out for their anatomical position and each node is histologically examined for evidence of metastasis. All the patients with more than four positive nodes are accepted for treatment and are treated either by postoperative radiotherapy or postoperative combination chemotherapy with methotrexate, 5-fluorouracil, mitomycin and cyclophosphamide in a bolus in one day. Patients receiving postoperative radiotherapy receive 3000-3500 rad to the drainage areas while those receiving chemotherapy receive a monthly bolus for the next year.

PROGRESS: About twenty-five patients have entered the study in each group. Early reports indicate that protracted chemotherapy may prevent or retard onset of systemic metastases.

165. POSTOPERATIVE RADIOTHERAPY AND CHEMOTHERAPY UTILIZING L-PAM IN PATIENTS WITH BREAST CANCER

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OBJECTIVE: To evaluate the effects of adding prolonged chemotherapy in patients with breast cancer.

APPROACH: Patients with one or more positive axillary nodes who undergo conventional radical mastectomy or modified radical mastectomy enter this study. Patients are randomly assigned to radiotherapy plus L-PAM and radiotherapy plus placebo. (1) L-PAM 0.15 mg/kg/day P.O. 5 days every 6 weeks, or (2) placebo in equivalent dosage form. Chemotherapy will be initiated two to four weeks postoperatively and will be given concomitantly with radiotherapy. Chemotherapy is to be terminated at the end of two years (16 courses) or upon the appearance of recurrent disease, whichever should occur first.

PROGRESS: Patients entered into the study in October 1976. As of October 1978, a total of 140 patients have been entered on study. There has not been sufficient time to produce conclusive information about the treatment effects. Longer follow-up time in all patients will be needed to obtain significant results.

166. TREATMENT OF SMALL CELL CARCINOMA OF THE LUNG WITH INTENSIVE CHEMOTHERAPY AND RADIATION THERAPY

Stewart, P., Bagley, C. M., Richardson, G., Wright, P., Fred Hutchinson Cancer Research Center, Division of Oncology, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

This project evaluates the complete response rate and survival of patients with small cell lung carcinoma treated with an intensive five-drug chemotherapy regimen, with the addition of localized radiotherapy for those with disease limited to one hemi-thorax. In addition, it will determine whether selected patients with extensive disease benefit from consolidation with high dose chemotherapy, total body irradiation and autologous marrow infusion.

167. TREATMENT OF SMALL CELL CARCINOMA OF THE LUNG WITH COMBINED CHEMOTHERAPY AND RADIOTHERAPY

Papac, R. J., Son, Y. H., Yesner, R., Kapp, D., Keohane, M., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology Section, *W. Spring St., West Haven, Connecticut*, 06516, United States of America

BACKGROUND AND RATIONALE: Recent studies of therapy for small cell carcinoma of the lung suggest that this tumor, known to be responsive to both chemotherapy and radiotherapy, is best managed by a judicious combination of these modalities.

In order to assess the efficacy of combined treatment in this disease, we have studied 75 patients seen at the Veterans Administration Hospital since 1970; of this group 20 had single agent chemotherapy; 18 had only radiation therapy (having refused other treatments or disappeared from follow-up). The other patients had cyclic chemotherapy with cyclophosphamide, vincristine and methotrexate as well as radiotherapy to the pulmonary lesion. From this experience we hope to improve the management by the following changes: first, replacing vincristine with a drug that appears to have improved response rate in small cell carcinoma, namely VP 16-213; second, to continue to give this form of chemotherapy during the period of radiotherapy to the pulmonary lesion; third, to administer chemotherapy initially to all cases (including those with radiotherapy; fourth to give chemotherapy following radiotherapy (2 cycles) as well; fifth, to randomly treat with whole brain irradiation the patients who appear disease free at one year, since central nervous complications are significant in these patients who prove to be 'long-term' survivors; sixth, in patients with restricted disease, if the primary tumor has not shown 50% reduction in size with the initial chemotherapy (3 cycles) after radiotherapy, the drug regimen will not be continued. Experience has shown that 3 drug cycles are adequate to be indicative of response.

168. COMBINED-MODALITY TREATMENT OF LIMITED SMALL-CELL CANCER OF THE LUNG

Belt, R. J., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *4801 Linwood Blvd., Kansas City, Missouri*, 64128, United States of America

OBJECTIVES: To determine if complete response rates (disappearance of all clinical evidence of active tumor for a minimum of 4 weeks) and survival in limited small-cell lung cancer can be improved using an intensive program of combined radiation therapy and chemotherapy. To determine the toxicity of such a regimen.

PLAN: Treat patients with limited small-cell lung cancer with intensive induction therapy using radiation and concomitant chemotherapy. Subsequent treatment will involve lower dose 'maintenance' chemotherapy for 1 year with intermittent intensive doses. Prophylactic whole-brain radiation therapy will also be administered.

RESULTS: To date 3 patients from the KCVAH have been entered on study. One patient died of a myocardial infarction after only 8 weeks and is not evaluable. At autopsy, however, this patient had no evidence of residual tumor. Two other patients achieved complete clinical remissions. One relapsed at 6 months, the other continues in complete remission on therapy at 6 plus months. Severe esophagitis associated with radiation therapy has prompted us to reduce the daily fractionated dose with better patient tolerance. The study will continue with a goal of 5-10 patients.

169. OAT-CELL CARCINOMA OF THE BRONCHUS - A STUDY OF PSYCHOSOCIAL RESPONSE IN PATIENTS RECEIVING CHEMOTHERAPY AND RADIOTHERAPY

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A comparative study is being carried out of the psychosocial response of patients when different treatment methods are used for oat-cell carcinoma of the bronchus. Although both chemotherapy and radiotherapy have adverse subjective effects during initial stages of treatment, it is not known how they compare with each other or with symptomatic treatment only.

Patients who have been randomly allocated to treatment groups depending on their clinical stage are being assessed, using a semi-structured interview procedure and a self-rating mood questionnaire, both before and during treatment.

170. STUDY OF NON-RESECTABLE LUNG CANCER PATIENTS TREATED WITH TP-1 AND WITH RADIOCHEMOTHERAPY

Aiuti, F., Luzi, G., LeMoli, S., Gallocurcio, C., Palmisano, L., Tropea, F., Universita degli Studi di Roma, Laboratorio di Immunologia, *Rome, Italy*

OBJECTIVE: Evaluation of survival in TP-1 treated patients with lung cancer in relation to controls (who undergo only radiochemotherapy). Observations on medullary toxicity of TP-1. Study of risk in neoplastic stimulation with TP-1.

APPROACH: The approach to this double-blind controlled study is fixed on immunological and clinical parameters. We study cellular and humoral arms of immunity, from specific and non-specific points of view. The random distribution of patients is defined by birth date (odd or even). Laboratory tests are executed by our group on days 0, 15, 40, 90 and 180 from the beginning of the study.

PROGRESS: By the end of 1979, 27 patients (14 treated with TP-1 and 13 with radiochemotherapy) had been studied and no significant difference was observed between the two groups.

171. THERAPEUTIC RESPONSE OF HUMAN TUMOR XENOGRAFTS

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Investigations will be performed mainly on xenografts of human tumors growing in immunosuppressed mice, and will be designed to elucidate the response of tumors to combined treatment with radiotherapy and chemotherapy. The usefulness of xenografts will be evaluated, concentrating upon carcinoma of the pancreas and testicular tumors. Comparisons will be made with Lewis lung carcinoma and with the response seen in patients. Emphasis will be placed on the search for in vivo evidence of potentiation between cytotoxic drugs and radiation. The results will be correlated with tumor size, both at the start of treatment and during regression. Parallel studies will be made of normal tissue reactions in lung, bone marrow and intestine, and in a subsidiary investigation the action of electroaffinic radiosensitisers will be tested on the xenografts.

172. MISONIDAZOLE COMBINED WITH IRRADIATION VERSUS RADIOTHERAPY ALONE FOR LOCALLY ADVANCED (STAGE IID) NON-OAT CELL LUNG CANCER (ABBREV)

Cox, J. D., Byhardt, R. W., Kun, L., Greenberg, M., Komaki, R., Gunn, W., Rangala, N., Wilson, J. F., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *5000 W. National Ave., Wood, Wisconsin*, 53193, United States of America

OBJECTIVES: To evaluate the effect of misonidazole in enhancing tumor control by irradiation at the primary site and the regional lymph nodes. To determine if the potential improvement of intrathoracic tumor control will prolong the disease-free interval and overall survival following radiation therapy. To evaluate the short-term and late sequelae of radiation therapy combined with misonidazole.

Radiotherapy plus misonidazole: Patient will receive radiotherapy 200 rad daily for five weekly fractions to deliver 5000 rad in five weeks. Additional 500-1000 rad boost to be delivered to gross residual tumor with reduced fields. Radiation will be preceded by misonidazole (1.0g/m2) twice weekly, total dose not to exceed 12 g/m2. The drug will be administered on Monday and Thursady and the irradiation will be given four hours later.

Radiotherapy: Irradiation as above without misonidazole.

173. 3-ARM STUDY USING COMBINATION CHEMOTHERAPY AND THORACIC IRRADIATION IN PARTIALLY RESECTED NON-SMALL-CELL CANCER OF THE LUNG (ABBREV)

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The purpose of this study is to determine whether radiotherapy alone, radiotherapy plus chemotherapy or chemotherapy alone is the superior approach to control of non-small-cell bronchogenic carcinoma after surgical treatment of extensive disease. Currently radiation therapy is the most commonly used modality for the post-surgical treatment of patients with non-small-cell lung cancer. Although radiation therapy has been shown to palliate the local symptoms in these subtypes of bronchogenic carcinoma, the problem of systemic spread has generally precluded its effectiveness in prolonging survivorship. The addition of chemotherapy to radiation therapy in one arm of this protocol is to determine whether a systemic modality in addition to radiation therapy might enhance both local and systemic control of this disease. The third arm utilizing chemotherapy alone will define whether systemic treatment alone is a good as as combined modality approach to these types of lung cancer.

174. CHEMOTHERAPY VS. CHEMO-RADIOTHERAPY IN LIMITED NON-SMALL-CELL LUNG CANCER

Einhorn, L. H., Bond, W. H., Williams, S., Stevens, E., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1481 W. 10th St., Indianapolis, Indiana*, 46202, United States of America

Patients with histologically proven non-oat cell lung cancer, which is limited in stage, will be randomized to receive irradiation alone, chemotherapy with Vindesine plus irradiation or chemotherapy with Vindesine alone. Of course, these patients will not be surgically resectable at the time that they are put on the study. Chest radiotherapy will consist of 4,000 rad, midplane tumor dose in 20 fractions to encompass the primary tumor with a 2 cm margin around the mediastinum. Supraclavicular nodes will be treated if they are involved. Chemotherapy will consist of Vindesine 3 mg/m2 given intravenously weekly for eight weeks and thereafter 3 mg/m2 given every two weeks.

Those patients undergoing both chemotherapy and irradiation treatment will receive them together as outlined above.

Response will be judged after the irradiation is completed in those patients receiving irradiation only, or after the first eight initial weeks of chemotherapy in those patients receiving chemotherapy plus irradiation or chemotherapy only. Patients progressing on chemotherapy alone will subsequently receive chest radiotherapy, if the disease is still limited. Those patients progressing on chest radiotherapy alone will receive chemotherapy. Patients progressing on chemotherapy plus irradiation will be off study.

175. TO DETERMINE WHETHER COMBINATION CHEMOTHERAPY AND RADIATION THERAPY PROLONGS SURVIVAL FOR PATIENTS WITH INOPERABLE LUNG CANCER (ABBREV)

Thomas, P. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Surgical Service, *820 S. Damen Ave., Chicago, Illinois*, 60612, United States of America

The palliative effect of radiation therapy versus combination drug chemotherapy with radiation therapy will be studied in a randomly selected group of patients with non-resected, non-small cell cancer of the lung. Criteria for entrance include pathologically demonstrated Stage III disease confined to the thorax. This is a multi-institutional cooperative study administrated by the Illinois Cancer Council.

176. CLINICAL TRIAL TO COMPARE RT PLUS CDDP, RT PLUS BLM AND RT ALONE IN SQUAMOUS CELL CARCINOMAS OF THE THROACIC ESOPHAGUS

Shanta, V., Krishnamurthi, S., Sastry, D. V., Krishnamurthi, R., Vasanthan, A., Rangakumar, G., Cancer Inst., Clinical Oncology Research Unit, *Adyar, Madras 600020, Madras, India*

OBJECTIVE: To evaluate the effectiveness of high energy photon radiation therapy per se versus a combination of radiation therapy plus BLM and RT plus CDDP in squamous cell carcinomas of the thoracic esophagus.

All histologically confirmed, previously untreated squamous cell carcinomas of thoracic esophagus without evidence of juxta-regional metastases or remote metastases or clinical invasion of the myocardium or the thoracic aorta will be random-

ized presently into three groups by the sealed envelope technique. Sub-randomization by sex will also be done. Randomization and evaluation will be blind and by code.

A total of 120 cases will be entered in the trial. Criteria of response will be 1) Short-term: favorable response - apparent total clinical healing of the lesion within the volume of irradiation at 8 weeks after end of radiation as established by radiology and fiber optic endoscopy. 2) Long-term: a) Recurrence-free rate within the volume of irradiation at 3 and 5 years. b) Survival NED at 3 and 5 years.

The project will extend over 3 years.

177. PALLIATIVE TREATMENT OF ESOPHAGEAL CARCINOMA WITH RADIOTHERAPY WITH OR WITHOUT CHEMOTHERAPY

Brunet, R., Richaud, P., Lagarde, C., Durand, M., Fondation Bergonie, Dept. of Medicine, *180 Rue de St. Genes, 33076 Bordeaux, France*

OBJECTIVES: 1) To determine if chemotherapy given before radiotherapy improves the results of treatment in non-surgical esophageal carcinomas. 2) To compare limited and large field radiotherapy in the same cancers.

APPROACH: Patients with non-resectable squamous cell esophageal carcinoma without metastasis are available for this trial. They are randomly allocated to receive one of the following three treatments: 1) large field radiotherapy alone; 2) chemotherapy followed by large field radiotherapy; or 3) chemotherapy followed by limited radiotherapy.

PROGRESS: A preliminary historical study was in favor of combination of the two treatments in 22 patients treated by radiotherapy plus chemotherapy. In November 1978, 15 patients were included in the present randomized trial.

178. COMBINED TREATMENT WITH RADIATION AND TRIETHYLENETHIOPHOSPHORAMIDE (THIO-THEPA) IN ADVANCED CANCER OF TONGUE AND FLOOR OF MOUTH

Constantin, E., Gonzalez, R., Gaitan, A., Instituto Nacional de Cancerologia, *Apartado Aereo #17.158, Calle 1 No. 9-85, Bogota, DE. Colombia*

OBJECTIVE: To determine the effectiveness of combined treatment with radiation and cytostatics in advanced cancer of the tongue and floor of the mouth.

MATERIAL: Patients with advanced cancer of the tongue and floor of the mouth (T3, T4, and/or N3).

METHOD: Two series of 3,000 rads in 2 weeks (10 fractions) alternating with three series of triethylenethiophosphoramide (thio-TEPA), each series of 60 mg/m2 divided into 6 daily doses per cycle.

179. LATE STAGE IV EPIDERMOID CARCINOMA OF THE ORAL CAVITY, LARYNX, AND HYPOPHARYNX

Niell, H. B., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee*, 38104, United States of America

This is a protocol investigating the use of radiotherapy and combination chemotherapy in patients with State IV epidermoid carcinoma of the oral pharynx, larynx and hypopharynx. This regimen will utilize the combination of methotrexate in fairly high dose, bleomycin, and cis-platinum, agents which are shown to be effective in the treatment of squamous cell carcinoma of the head and neck. This will be followed by 4000-5000 rads to the area, over 4-5 weeks. At the end of said treatment the possibility of surgery or follow-up care will be evaluated. It is, therefore, hoped that the results of this regimen will enable us to learn more about the ability of combination chemotherapy and radiotherapy to make patients who are initially inoperable, operable at a later date and, therefore, increase survival and cure.

180. 125I, 5-FU, AND EXTERNAL RADIOTHERAPY FOR PANCREATIC CANCER

Dobelbower, R. R., Medical College of Ohio at Toledo, School of Medicine, Dept. of Radiology, *Box 6190, Toledo, Ohio*, 43614, United States of America

The overall objective of the proposed research is to improve survival and palliation for patients with locally unresectable adenocarcinoma of the pancreas.

Of all the patients diagnosed with adenocarcinoma of the pancreas, only about 10% are candidates for definitive surgery. Approximately half of the remaining patients are considered unresectable because of the local extent of disease rather than distant metastases. At present, almost all of these patients die of cancer. The proposed project addresses this group of patients with a combination of three treatment modalities that have previously shown promise in this disease: interstitial implantation of radioactive sources into the tumors, precision high dose (PHD) external beam radiotherapy, and 5-fluorouracil (5-FU) adjuvant chemotherapy. Forty-five patients with locally unresectable pancreatic carcinoma will be studied over the course of 3 years. Pre-treatment: The local and distant spread of disease will be studied extensively, as will the status of organs adjacent to the pancreas. Intraoperative interstitial implants of 125I will deliver local tumor doses of approximately 14,000 rad. PHD external beam radiation therapy from an 18 MV linear accelerator will deliver 6000 rad in 7 weeks to the tumor plus a margin of 1-2 cm. Subsequent adjuvant 5-FU will be given weekly intravenously in a dose of 500 mg/m2. Patients will be followed regularly and studied with regard to the local toxic effects of combined modality therapy. Local toxicity will be analyzed as a function of total combined radiation dose. Patient survival will be compared to that of patients treated by PHD therapy alone and to historical controls.

181. ADJUVANT COMBINATION THERAPY OF RESECTABLE ADENOCARCINOMA OF THE COLON WITH WHOLE-LIVER IRRADIATION AND 5-FLUOROURACIL

Ramming, K. P., Stabile, B. E., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Surgical Service, *Wilshire & Sawtelle Blvds., Room 209, Los Angeles, California*, 90073, United States of America

Large bowel carcinoma afflicts more patients than any other malignant disease in the U.S. Survival rates following surgery have reached a plateau. The present study was designed to determine whether additional therapy after surgery would improve survival in patients with colon cancer. The high incidence of hepatic metastases following curative surgical resections of colon cancer has prompted the initiation of this study. This investigation is a prospective randomized clinical trial designed to compare hepatic irradiation and 5-fluorouracil with a control arm following resection. The effectiveness of this study will be evaluated in patients with adenocarcinoma of the colon with poor prognosis (Dukes' B2 and C lesions) who have undergone curative resections. Patients will be randomized and begin treatment within 7 weeks after colon resection. Patients who are randomized into the control group will receive no additional treatment but will be closely followed for evidence of disease recurrence up to five years after diagnosis. Patients randomized to receive treatment will receive radiation therapy (2100 rads) to the liver over a 2 1/2 week period. 5-FU will be administered on the first 3 days of radiation treatments and will again be given at 2 and 6 weeks after radiation is completed for 5 consecutive days each time. Patients will be closely followed for evidence of disease recurrence up to 5 years. Immunological testing and CEA will be performed on all patients participating in this study. Hepatic radiation and 5-FU have been previously utilized for treatment of well established liver metastases from colorectal primaries with reported good to excellent palliation. A pilot study at Mayo Clinic utilized the proposed treatment plan without adverse effect. The favorable results seen with palliation and the logic of this approach warrant further investigation.

182. ADJUVANT COMBINATION THERAPY OF RESECTABLE ADENOCARCINOMA OF THE COLON WITH WHOLE-LIVER IRRADIATION AND 5-FLUOROURACIL

Kaplan, R. S., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Oncology Branch, *Baltimore, Maryland*, 21201, United States of America

A prospective randomized controlled study of liver-directed and systemic adjuvant therapy in patients with high risk colon (excluding rectal) cancers is being carried out by the

Gastrointestinal Tumor Study Group. Patients are randomized to no adjuvant therapy or to 2100 R of liver irradiation combined with 3 days of IV 5-FU. Forty patients have been entered since the study was begun in August, 1979. No conclusions regarding efficacy can be made at this early data. Myelosuppression has been more striking than expected and, though no deaths have occurred, the 5-FU dose has been modified.

183. POSTOPERATIVE RADIATION AND CHEMOTHERAPY FOR RECTAL CARCINOMA (ABBREV)

Goldman, L. I., Golinger, R. C., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Surgical Service, *510 E. Stoner Ave., Shreveport, Louisiana*, 71130, United States of America

OBJECTIVES: This study will compare the length of disease-free interval survival of patients who had a curative resection of adenocarcinoma situated at or distal to the peritoneal reflection (rectum) with that of patients who are receiving systemic chemotherapy or regional radiation therapy in addition to operation.

RESEARCH PLAN AND METHODOLOGY: The groups will be randomized into those undergoing operation alone, operation followed by post-operative radiotherapy or operation plus systemic combination chemotherapy which includes 5-FU, Methyl CCNU and Vincristine cycled at ten week intervals x 8. The end points to be used for the statistical studies will be: a. evidence of treatment failure; b. survival; c. morbidity. This study is part of a national surgical adjuvant program.

FINDINGS: To date, two eligible patients have been acquisitioned. One has undergone the required radiation therapy; the other patient has a Dukes A lesion which is being followed, following surgical therapy.

184. ABLATIVE TREATMENT OF SOLID TUMORS WITH RESCUE AUTOLOGOUS BONE MARROW REINFUSION

Haanen, C., Wagener, D., Wessels, J., Zwinkels, C., de Witte, T., University Hospital of Nijmegen, Div. of Hematology, *Geert Grooteplein 10, 6525 GA Nijmegen, Netherlands*

Patients with bad risk solid tumors, e.g., oat cell, Ewing's sarcoma, immunoblastomas, etc., will be treated with high-dose radiochemotherapy motherapy. The aplastic phase will be covered/rescued by reinfucion of autologous cryopreserved bone marrow which has been treated by radiochemotherapy in order to eliminate metastatic cells while preserving progenitor cells. Cell separation studies, viability studies, bone marrow culturing and clinical studies are planned.

185. CELL PROLIFERATION IN EPITHELIAL TISSUES - GROWTH CONTROL, CARCINOGENESIS AND RESPONSE TO IRRADIATION AND CYTOTOXIC CHEMOTHERAPY

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OBJECTIVES: a) To identify and quantify stem cells in the small intestinal crypt. b) To analyze aspects of the control of cell proliferation in the intestine with special reference to the size of the functional compartment. c) An analysis of cell line specific growth control substances in the intestine. d) The evolution of clonogenic tumor cells during carcinogenesis in the intestine. e) The selectivity of cell death in proliferating and resting in vivo cell populations.

APPROACH: The approach will be mainly via orthodox cell kinetic techniques involving metaphase arrest, microdissection and autoradiography, and clonogenic assays involving microcolony analysis of the intestine and in the prostate gland.

186. CLINICAL LABORATORY ASSESSMENT OF A COMBINATION OF DRUGS WITH RADIATION AND OTHER TREATMENT MODALITIES

Bleehen, N. M., Medical Research Council, Clinical Oncology & Radiotherapy Unit, *Hills Rd., c/o Medical School, Cambridge CB2 2QH, England, United Kingdom*

The objective is laboratory and clinical studies in combined modality treatment with drugs, radiotherapy and hyperthermia. Particular attention is being paid to hypoxic cell radiosensitizers and the interaction of heat and cytotoxic agents.

187. THC VERSUS COMPAZINE IN RADIATION THERAPY ONCOLOGY PATIENTS

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No summary has been provided to the Smithsonian Science Information Exchange.

188. COMBINED INTRA-ARTERIAL CHEMOTHERAPY-RADIATION THERAPY CLINICAL RESEARCH

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This is part of a broader project. A summary of this subproject is not available.

2. RADIOTHERAPY AS AN ADJUVANT IN HORMONAL THERAPY AND IMMUNOTHERAPY

189. STAGE I FIGO ENDOMETRIAL CARCINOMA - RADIO-SURGICAL TREATMENT AND PROGESTIN THERAPY IN RELATION TO RISK FACTORS (ABBREV)

Mangioni, C., Periti, P., Universita degli Studi di Milano, Clinica Ostetrica e Ginecologica IV, *12 via Commenda, 20122 Milan, Italy*

Objectives of the present Clinical Study of Stage I (FIGO) endometrial cancer are as follows: 1) Accurate evaluation of neoplastic extension by anatomo-radio-surgical staging; 2) thorough investigation of tumor and host risk factors; 3) objective assessment of the value of post-operative external irradiation in high-risk cases; 4) collection of a large number of cases stratified according to prognostic factors and allocated at random to progestin treatment so that effectiveness of adjuvant medroxyprogesterone acetate can be statistically assessed, at least for the entire population studied; 5) assessment of progesterone and estrogen receptors in a pilot series, with possible correlations with grade, histotype and clinical response, as well as with MAP plasmatic levels.

The Protocol of the Study has been discussed by both principal and affiliated units in a series of meetings held in Milan, Brescia, Florence and Rome in order to collect, define, and unify all emerging instances of cooperation and to select the 19 cooperating Units as follows: II, III, IV and V Cl. Ost. Gin. Univ. Milano; I and II Cl. Ost. Gin. Univ. Torino; Cl. Ost. Gin. Univ. Genova, Pavia and Padua; I and II Cl. Ost. Gin. Univ. Bologna; Cl. Ost. Gin. Univ. Cattolica S. Cuore di Roma, Ist. Regina Elena, Roma, II Cl. Ost. Gin. Univ. Roma; I and II Cl. Ost. Gin.. Univ. Bari; Cl. Ost. Gin. Univ. Pisa, Catania, Florence.

After a further discussion, a common data base has been agreed upon and a modular chart for the collection of data has been elaborated and printed. A six-month pilot study is to be started February 1, 1980.

190. EARLY BREAST CANCER - THE USE OF OVARIAN IRRADIATION AND PREDNISONE AS ADJUNCTIVE THERAPY AFTER MASTECTOMY

Hayward, J. L., Bulbrook, R. D., Meakin, J. W., Allt, W. E., Beale, F. A., Brown, T. C., Bush, R. S., Clark, R. M., Fitzpatrick, P. J., Hawkins, N. W., Jenkin, R. D., Pringle, J. F., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Over a period of eight years, all women with early breast cancer who were referred to the Princess Margaret Hospital in Toronto for post operative radiotherapy were entered into a trial on the use of prophylactic ovarian irradiation and prednisone. Those women aged 45 and over were randomly allocated to three groups: group 1, no treatment; group 2, ovarian irradiation, group 3, ovarian irradiation plus prednisone. Patients aged under 45 were allocated only to groups 1 and 2. Recurrence times and survival in these patients were determined by external review.

It has been shown that in those women aged 45 or over, but who are still premenopausal, the use of ovarian irradiation and prednisone confers a highly significant degree of benefit in

terms of both recurrence and survival. The degree of benefit induced by ovarian irradiation alone was not as pronounced. No benefit was conferred by either treatment method in patients who were postmenopausal.

The review of these cases is being undertaken biennially and will next be done in 1981. A further analysis of the results will then be carried out.

191. COMBINED IRRADIATION AND LUCANTHONE THERAPY (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

192. NON-SPECIFIC ADJUVANT IMMUNOTHERAPY IN THE RADIATION TREATMENT OF STAGE III CERVICAL SQUAMOUS CARCINOMA (ABBREV)

Shanta, V., Krishnamurthi, S., Girija, P., Nagarajan, B., Cancer Inst., Radiation Oncology Unit, *Adyar, Madras 600020, Madras, India*

Stage III cervical squamous cell carcinomas constitute 76% of all cervical cancers seen at the Institute. Radiotherapy per se has achieved so far only a 36% five-year disease-free survival in our series. This study was undertaken to evaluate whether a non-specific immunogenic agent like C. parvum would enhance cervical as well as pelvic tumor resolution.

Forty cases were entered into the trial, 20 study subjects and 20 controls. All were Stage III cervical squamous cell carcinomas. All received radiation therapy using a Cobalt-60 beam through 3 portals to deliver a mean tumor dose of 6,000 rads in the para-cervical cube, in about 6 weeks. No intracavitary therapy was used in any of these cases.

C. parvum was administered in the following protocol to the study group: 1) 20 mg I.V. infused in physiological saline one week prior to radiation; 2) 4 mg in physiological saline as I.V. bolus and 4 mg as intraparametrial injection weekly during the course of the radiation therapy; 3) 4 mg of C. parvum as intravenous bolus weekly for 8 weeks after the end of the radiation therapy.

The controls received only physiological saline on the same protocol as C. parvum in the study cases.

The criterion of favorable response was total clinical healing of the pelvic tumor within the volume of irradiation at 8 weeks after the end of the radiation therapy. The evaluation was blind.

A favorable response was obtained in 66.66% of the study cases and 62.5% of the controls. There was no therapeutic advantage in the C. parvum group. Apart from a pyrexial reaction on the day of the C. parvum injection no other toxicity was noticed.

193. BRONCHOGENIC CARCINOMA - IMMUNOLOGIC PROFILE, RADIOTHERAPY AND IMMUNOTHERAPY

Stefani, S. S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Therapeutic Radiology Service, *5th Ave. & Roosevelt Rd., Hines, Illinois*, 60141, United States of America

This study compares the effect of the BCG immunotherapy given in conjunction with radiotherapy (BCG-RT) with that of radiotherapy (RT) alone. Patients with advanced bronchogenic carcinoma were used in the study and were randomized into different treatment groups. A series of immunological tests, such as the skin tests for four antigens, the total T, active T and B cell assays, and the PHA stimulation of lymphocytes were done routinely on all patients. The immunological profile was obtained following the BCG and RT therapy.

To date, 106 patients have been entered on the BCG immunotherapy protocol, 23 were dropped due to either patient refusal or other reasons specified in the protocol, 40 were treated with BCG plus radiotherapy (BCG-RT) and 43 were treated with radiotherapy alone (RT).

The median survival time of the BCG-RT group is 286.3 days, while for the RT group it is 361.9 days. The difference is not significant statistically. Immunological tests done have been analyzed with no significant findings to this date. The results of this study are being tabulated and will be published soon.

194. LEVAMISOLE, RADIATION AND INTRATUMORAL BCG THERAPY FOR ADVANCED LUNG CANCER

Papac, R. J., Matthay, R. A., Kapp, D. S., Fischer, J. J., Baue, A. E., Reynolds, H. Y., Raymond, L., Carter, D., Curtis, A., Loke, J., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology/Oncology Service, *W. Spring St., West Haven, Connecticut*, 06516, United States of America

This project is a study to determine the effects of immunotherapy as an adjunct to radiotherapy in advanced bronchogenic carcinoma, non-anaplastic cell types. The forms of immunotherapy to be used are levamisole and levamisole with intratumoral BCG. Patients to be included in this study will be those with disease limited to the hemithorax with or without ipsilateral scalene node involvement and patients with stage I or II disease who are medically inoperable. The study will include a control group undergoing radiotherapy alone.

This study will involve patients in three institutions in this area, the Yale-New Haven Hospital, St. Raphael's and the Veterans Administration Hospital.

195. IMMUNO-STIMULANTS IN LOCALIZED RADIATION THERAPY

Wara, W. M., University of California, San Francisco Campus, School of Medicine, Dept. of Radiation Oncology, *551 Parnassus Ave., San Francisco, California*, 94122, United States of America

GOAL: To document the immunosuppresion which occurs following radiation therapy to determine if a therapeutic advantage can be achieved by the addition of immunotherapy (thymosin) to the conventional treatment given for squamous cell carcinoma of the head and neck region and esophagus.

APPROACH: Both groups of head and neck and esophageal cancer patients will receive radiation therapy and/or surgery as treatment. Patients will then be randomized to receive thymosin or placebo in addition to standard treatment. All patients will be monitored with immunologic tests to measure antibody-mediated and cell-mediated immunity at regular intervals. The data will be analyzed for local disease recurrence, metastatic disease, and survival difference in the treatment groups.

3. OTHER COMBINATION MODALITIES

196. ADVANCED BREAST CANCER - THE USE OF COMBINED RADIOTHERAPY, CHEMOTHERAPY AND ENDOCRINE THERAPY IN THE TREATMENT OF LOCALLY ADVANCED TUMORS

Hayward, J. L., Rubens, R. D., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Patients with Stage III breast cancer are usually treated with radiotherapy. The prognosis is poor, over half of patients developing distant metastases with a median survival of only 25 months. If the prognosis of Stage III breast cancer is to be improved, systemic treatment may be needed in its planned initial management.

A pilot study showed that chemotherapy and radiotherapy can be combined safely (ICRF Scientific Report 1978 - report 326). In a historical comparison of this study with patients treated previously by radiotherapy alone (ICRF Scientific Report 1977 - report 289), there was a better response rate and longer duration of response for patients receiving the combined therapy (European Journal of Cancer, in press). In view of these encouraging results, a 2 x 2 factorial design trial has been planned in which radiotherapy alone will be tested against cytotoxic chemotherapy alone, endocrine therapy alone, and combined cytotoxic and endocrine therapy. This trial is being carried out in conjunction with the European Organization for Research into the Treatment of Cancer (EORTC) and endocrine studies will be carried out in collaboration with the Clinical Endocrinology Laboratory.

197. ADJUVANT RADIO-, CHEMO- AND IMMUNOTHERAPY OF OPERABLE BREAST CANCER

Grohn, P. T., Heinonen, E. O., Klefstrom, P. S., Tarkkanen, J. O., Helsinki University Central Hospital, Dept. of Radiotherapy, *Haartmaninkatu 4, 00290 Helsinki, Finland*

OBJECTIVE: The aim of this study is to evaluate the value of post-operative radiotherapy, chemotherapy, combined radio- and chemotherapy and all of the above with non-specific immunotherapy with levamisole.

APPROACH: Normally, operated on breast cancer patients with stages II of III receive postoperative regional radiotherapy. It is known that mostly in cases with state III and very often in cases with stage II breast cancer the spreading of the cancer has already taken place at the time of diagnosis for these patients the value of local radiotherapy is questionable, because radiotherapy affects local recurrences but not the life expectancy of the patients. The early results of adjuvant chemotherapy as obtained by Bonadonna and others are encouraging. In our study the patients are randomized to various treatment groups and levamisole is administered double-blindly.

PROGRESS: Stage II breast cancer patients are randomized to two treatment groups, both receiving postoperative radiotherapy with levamisole or placebo. The data are being evaluated . Stage III breast cancer patients are randomized to following treatment groups: postoperative radiotherapy or postoperative chemotherapy or both, together levamisole or placebo.

The patients are examined as to recurrent disease, immunological status, routine laboratory examinations.

The research with stage III breast cancer patients is in progress.

198. CONSOLIDATION OF METASTATIC BREAST CARCINOMA WITH CYCLOPHOSPHAMIDE (TOTAL BODY IRRADIATION AND AUTOLOGOUS BONE MARROW TRANSPLANTATION)

Buckner, C. D., Appelbaum, F., Smith, J. W., Stewart, P., Fred Hutchinson Cancer Research Center, Division of Oncology, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

This project is to ascertain the therapeutic effectiveness of chemoradiotherapy and autologous marrow infusion as consolidation therapy in patients with metastatic breast cancer who are responsive to chemotherapy or hormonal therapy.

Premenopausal and perimenopausal women with metastatic disease without involvement of the iliac crest bones will have bone marrow storage followed by conventional chemotherapy or hormonal therapy. When a measurable response has plateaued, the patient will be consolidated with high dose cyclophosphamide, 1000 rad total body irradiation and autologous marrow reinfusion. No maintenance therapy will be given to those patients who attain a complete remission. The value of immunologic reconstitution with and without stored peripheral blood mononuclear cells will also be assessed.

199. STAGE I AND II CARCINOMA OF THE BREAST - TOTAL MASTECTOMY VERSUS EXCISIONAL BIOPSY AND DEFINITIVE IRRADIATION (ABBREV)

Lichter, A. S., de Moss, E. V., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Radiation Oncology Branch, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

OBJECTIVE: This study seeks to discover whether therapy which leaves the breast intact (lumpectomy followed by radistion) is or is not equal in terms of patient survival to standard mastectomy techniques for clinical Stage I and II carcinoma of the breast. Patterns of local, regional, and distant recurrence will also be studied.

APPROACH: Patients 70 years of age or younger will undergo a complete staging work-up and then be randomized to therapy with mastectomy or with lumpectomy, axillary dissection, and definitive irradiation. After external beam radiation, an implant will be used to boost the local tumor bed. No irradiation will be used on the surgically treated patients. All patients with positive nodes will receive adjuvant chemotherapy.

PROGRESS: Thirty patients have enrolled in the study within its first year. Patient accrual is proceeding.

200. TREATMENT OF LIMITED SMALL CELL BRONCHOGENIC CARCINOMA - CHEMOTHERAPY ALONE OR WITH RADIATION THERAPY WITH OR WITHOUT THYMOSIN

Cohen, M. H., Minna, J. D., Bunn, P. A., Ihde, D. C., Matthews, M. J., Fossieck, B. E., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Medical Oncology Branch, *50 Irving St. N.W., Washington, District of Columbia*, 20422, United States of America

Thirty patients are currently entered, 15 on each arm.

There has been no unexpected toxicity. Nineteen patients have completed one year of treatment. Four of these 19 patients who have received chemotherapy plus radiation therapy are alive and disease-free, while one patient treated with chemotherapy alone has achieved this status.

It is planned to continue accrual onto this study for at least one more year.

201. THERAPEUTIC CONTROLLED STUDY OF PEDIATRIC GLIOMAS

Ambrosio, A., Colangelo, M., Palmieri, A., Catalano, E., Capece, W., Licenziati, F., Ospedali Riuniti per Hambini di Napoli, Dept. of Pediatric Neurosurgery, *Via Mario Fiore 8, 80131 Naples, Italy*

The main goal of the research consists of determining differences between two different combined treatments of the gliomas (Surgery plus Radiotherapy plus Chemotherapy versus Radiotherapy plus Surgery plus Chemotherapy). The evaluation will be made in terms of survival and a useful recovery.

Furthermore, the administration of radiation therapy and of chemotherapy, according to the usual dosages, will be critically estimated by studying their incidence on these parameters: Intracranial pressure (ICP), bioelectrical cerebral activity (EEG), and reduction in the volume of neoplasm.

In the case of pre-surgical irradiation, the approach is performed through the pre-operative evaluation, consisting of CT-scan, monitoring of ICP and EEG, followed by intraoperative observation of a certain number of facors, which are: 1) reduction in the volume of neoplasm, 2) reduction in the bleeding and a much easier hemostasis, 3) a much easier condition for removing the neoplasm from the surrounding area, and 4) a much easier fragmentation of the tumoral mass.

In the case of post-operative irradiation, the approach is made during the follow-up time and it employs the described procedure of evaluation (CT-scan, ICP and EEG monitoring) according to a scheduled program.

202. SURGERY COMBINED WITH IRRADIATION AND CHEMOTHERAPY IN ESOPHAGEAL CANCER

Grandval, C. M., Hospital Nacional de Gastroenterology Bonorino Udaondo, Servicio de Cirugia, *Caseros 2061, Buenos Aires, Argentina*

OBJECTIVE: There is a very high incidence of esophageal cancer in Argentina. In the surgical service at our hospital, this incidence is reflected in a growing increase in cases every year. Between 1960 and 1970, we observed a low index of operability (60 percent) and a low incidence of resectability (40 percent). Five years ago, we initiated a project designed to increase the indices of resectability and cure.

METHOD: Patients with esophageal cancer in the middle third or inferior third: a histologic diagnosis of epidermoid carcinoma; complementary studies indicating a resectable lesion (bronchoscopy, thoracic X-ray, hepatic scintigram, etc.). Patients able to undergo surgery receive a combination of telecobalt therapy plus bleomycin. The lesion is located within a metal frame to centralize the radiation. The recommended dose is 250 rads to the tumor every day for 10 consecutive days. Every other day, between 30 and 60 minutes before cobalt therapy, 7.5 mg bleomycin is injected, the total dosages equaling 52.5-60.0 mg bleomycin and 2500 rads. The patient undergoes surgery immediately after treatment.

In the case of esophageal cancer of the middle third, a total esophagectomy is performed in one or two operations with reconstruction of the pathway of cervical esophagogastremic anastomosis with retrosternal ascent of the stomach. In cancer of the inferior third of the esophagus, a partial esophagogastrectomy is performed with left infra- or supra-aortic anastomosis.

The resected tissue is studied in detail to observe structural, morphological, cellular, interstitial or nuclear changes that might be attributed to the chemotherapy or radiotherapy. Based on the experience of over 350 esophageal cancers treated over the last 20 years, a comparison is made of results and histolgic studies in patients treated with radiotherapy alone or with bleomycin alone. (Translated)

BIBLIOGRAPHIC REFERENCES: International Symposium on Bleomycin. XII International Cancer Congress, Buenos Aires, 1978.

203. PHASE I STUDY OF INTRA-OPERATIVE RADIATION THERAPY FOR ABDOMINAL AND PELVIC MALIGNANCIES

Tepper, J., Sindelar, W., Glatstein, E., Rosenberg, S., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Radiation Therapy Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

OBJECTIVE: To study the ability to combine intra-operative radiation therapy with radical surgery for various abdominal a .d pelvic malignancies.

The plan of the Phase I study is to take patients who had conventionally unresectable or marginal resectable intra-abdominal and pelvic carcinomas and to perform a maximal surgical resection. This was followed by a single dose of 2000 rad of intra-operative radiation therapy, in order to improve the local control and thus the cure rate of these tumors. Six patients have been irradiated to date. The tolerance of this radiation therapy combined with radical surgery seems to be acceptable. There have been no major complications attributable to the radiation therapy. No statement can be made to date as to the efficacy of this treatment with regard to local control of tumor.

204. BLADDER CANCER - PREOPERATIVE IRRADIATION, CYTOSTATICS AND SURGERY

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OBJECTIVE: To increase survival in patients with bladder cancer classified as: T1N0M0 (A); T2N0M0 (B); T3N0M0 (B2C); T2N1M0 - T2N2M0; T3N1M0 - T3N2M0.

METHOD: Preoperative irradiation and cytostatics (thiophosphoramide and 5-fluorouracil). Surgery: electrocoagulation, transurethral resection, partial cystectomy, total cystectomy with or withcut regional ganglionar dissection.

205. ONE INTRACAVITARY CO60 INSERTION PLUS RADICAL SURGERY VERSUS FULL RT IN STAGE IB, IIA, IIB UTERINE CERVICAL SQUAMOUS CELL CARCINOMA

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OBJECTIVE: The treatment of carcinoma of the uterine cervix is fairly well established. In cases when a recurrence occurs, however, it is usually in the cervix or the imr ediately adjoining parametrium in early cases. Radical surgery which then becomes indispensable results in considerable urinary and pelvic morbidity. It was felt that if after one intracavitary Co60 insertion, which secures considerable regression of the local tumor in the cervix and the adjoining parametrium, radical surgery is performed with a removal of a smaller cuff of vagina and a more limited ureteric dissection, is likely to yield a better survival rate and much higher recurrence-free rate.

A controlled clinical trial to ascertain information in this regard has not so far been reported, to our knowledge. It is proposed to conduct a randomized controlled clinical trial to evaluate the two procedures outlined. All stage IB, IIA and IIB cervical cancers will be entered in the trial in the next three years. They will be concurrently randomized by stage by the sealed envelope technique and a 3-year and 5-year pelvic recurrence-free rate and survival NED will be assessed. It should be mentioned here that all cases receiving only radiotherapy will also have an extraperitoneal pelvic lymphadenectomy done.

The study will also help to estimate occult nodal metastases in these cases and compare the morbidities in the two modalities of treatment.

The trial is now under way.

206. EVALUATION OF SURGERY, RADIOTHERAPY AND IMMUNOTHERAPY IN STAGE B AND C CARCINOMA OF THE PROSTATE

Mira, J. G., Lamm, D. L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Radiology Service, *San Antonio, Texas*, 78284, United States of America

The objectives of this report are to compare the effectiveness of surgery plus immunotherapy against surgery plus radiotherapy in the local control of prostatic carcinoma in clinical Stages B and C with positive nodes. We also want to compare the effectiveness of two modalities of local radiotherapy (implant and external beam), as well as the meaning of positive biopsies after radiotherapy, and to correlate the assays of immunocompetence with the clinical course of the various treatment modalities.

The research plan is to randomize patients with Stage B to surgery plus immunotherapy, or surgery plus radiotherapy. If the second randomization was chosen, patients would recieve surgery alone if the nodes in the pelvis were negative, or surgery and post-operative radiotherapy if these nodes were positive. For Stage C, the same randomization (surgery plus immunotherapy vs. surgery plus radiotherapy) was done. However, if surgery plus radiotherapy was chosen, further randomization will be done to receive either seeds to the prostate with iodine 125 or external beam.

Unfortunately, our accrual of cases has been very small. Approximately 9 cases have been accrued so far. No case has been found to be suitable for the implant with iodine 125 seeds. Hence, no real findings are available so far.

The protocol does not require any funding; it is a tool to allow the patients with carcinoma of the prostate to receive a uniform treatment at the University of Texas Health Science Center at San Antonio. Hence, although the accrual has been very disappointing, we still would like to keep it open, hoping that eventually, in the future, the accrual will increase.

No new developments have been reported in the literature during the last year to show that our protocol needs to be changed.

207. COMBINED MODALITY TREATMENT OF CANCER PATIENTS

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This application seeks support for a conference on Normal Tissue Effects with Combined Modality Treatment of Cancer Patients. The meeting is planned for April 29-30, 1981, at Amelia Island, Florida, or a similar site. This will be the eighth in a series of meetings designed to improve radiation therapy through the application of advances in the basic sciences and advances in other fields. The tolerance of critical and normal tissues represents the most common limiting factor in the attainment of long-term control in patients with malignant disease. In recent experiments it has been recognized that when radiation therapy is combined with multi-drug chemotherapy, the toxicities in normal tissues are accentuated, not only in general, but particularly in the volume being irradiated. This meeting will strive to develop a better understanding of the problems facing the clinician in this area of multi-modality cancer management. In addition to the immediate benefit derived from the interaction among investigators, this meeting will form the nucleus of a large scale national conference to be held at a later date, which will be directed to the broad community involved in clinical trials as well as clinical practice in cancer management.

208. EVALUATION OF SUPERVOLTAGE THERAPY

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Recently, increasing emphasis has been placed on combining radiotherapy with surgery and/or chemotherapy. The combinations of these three modalities of treatment are innumerable. Combinations of surgery and radiotherapy range from radical surgery with radiotherapy as an adjuvant to various degrees of

diminished surgical procedures including excision of only the gross tumor mass. The management of breast cancer provides an example where the complete spectrum of combinations is presently utilized. Radiotherapy can be given before or after surgery as can chemotherapy. Recently, there has been renewed interest in the use of radiosensitizers and combinations of radiotherapy with hypothermia.

In order to provide a solid data base, there must be a critical analysis of the results of treatment. Usually, meaningful data can be obtained only by continual accession of cases, accurate evaluation and coding, constant updating, and multivariate analysis. The data must be coded and analyzed not only for patients treated by radiotherapy, but also for those treated by surgery and/or chemotherapy. Thus, for comparison, all patients seen and treated in the same disease category are included. The analysis includes not only survival rates, but also causes of failure and complications.

Between 1948 and December 1978, approximately 33,000 patients have been treated by supervoltage radiotherapy alone or in combination with intercavitary or interstitial implants. Of the treated patients, more than 24,500 cases have been coded.

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209. SURGICAL AND RADIATION THERAPY, ADJUVANT IMMUNOTHERAPY IN LUNG CANCER (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

E. RADIOSENSITIZING AGENTS AND PROCEDURES

210. RADIOTHERAPY OF CANCER OF THE BLADDER, BRONCHUS, AND CERVICAL UTERI IN COMBINATION WITH RADIOSENSITIZING DRUGS

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A randomized clinical trial with misonidazole, a drug used for specific radiosensitization of hypoxic cells of tumors, in combination with daily multifraction radiotherapy (DMF) began in 1979 and included patients with 1) transitional bladder carcinoma, stage T3 NX MO, 2) non-oat cell bronchial carcinoma, non-resectable, 3) carcinoma of the cervix uteri, stage III. To test: the local and general tolerance of misonidazole in combination with DMF radiotherapy, particularly neurotoxicity; the immediate response of the tumor, evaluated as tumor mass volume reduction; the length of local tumor control, the quality of life and the survival of patients. For each side, patients were at random assigned to a study or to a control group. Study group patients were administered misonidazole every day, 650-800 mg/sq. m., 3 hours before the first session of radiotherapy, 1Gy 3 times every day with an interval of 4 hours between sessions, for 3-3 1/2 weeks. Control group patients received placebo instead of misonidazole; radiotherapy was administered following the same scheme. On the whole, 20 patients from the study group and 18 from the control group have been evaluated. The local tolerance to radiation treatment alone or in conjunction with misondazole was good, without significant differences between groups. 11/20 patients treated with misonidazole showed toxic symptoms (rash 1 p., oral mucositis 1 p., ototoxicity 1 p., sensorial peripheric neuropathy 6 pts.) which appeared 2-3 weeks after the beginning of treatment and persisted for 4-15 weeks. For all neoplastic sites tumor shrinkage was more frequent and larger in the misonidazole plus RT group than in the placebo plus RT group. A study of drug concentration in blood and in normal and neoplastic tissues in bladder carcinoma patients after total cystectomy has begun.

211. TOXICITY OF NITROIMIDAZOLE HYPOXIC RADIOSENSITIZERS

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Although misonidazole is now in the early stages of clinical trials for use as a hypoxic radiosensitizer in conjunction with radiotherapy, it is already apparent that its toxicity limits its use to levels much below those required for the optimal radiobiological response. Studies in progress demonstrate that misonidazole is reduced to unidentified derivatives that are much more toxic than the original compound. E. coli suspensions are a convenient source of these metabolites that can also be found in the blood, urine and feces of patients being treated with misonidazole. In this project several different endpoints of toxicity will be studied in E. coli to identify the toxic products and better understand the mechanism of toxicity. Useful endpoints being used in our lab include mutagenicity, killing of wild-type and DNA repair defective strains, and inhibition of beta-galactosidase induction. Various compounds have differential effects on these endpoints indicating that radiosensitizing compounds do not necessarily have these side effects. We anticipate that the studies in progress will lead to a better understanding of the toxicity of misonidazole and the development of less toxic hypoxic radiosensitizers.

212. LOCALLY UNRESECTABLE OSTEOGENIC SARCOMAS

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The purpose of this project is to study the hypoxic cell radiosensitizer misonidazole in conjunction with radiation therapy in the treatment of locally unresectable osteogenic sarcoma and chondrosarcoma. Patients who have a local neoplasm for which no radical surgery can be successfully undertaken will be treated with fractionation radiation therapy in conjunction with intravenously administered misonidazole. Because of the small number of patients who are appropriate for such a study, this will be a one-armed study. Following completion of radiation therapy, combination chemotherapy will be administered to patients with osteogenic sarcoma with high grade neoplasms. Following completion of all treatment, survival, freedom from relapse, and complications of treatment will be carefully assessed.

213. STUDY OF RADIATION SENSITIZERS IN CARCINOMA OF THE ESOPHAGUS

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The purpose of this project is to study radiation sensitizing compounds and their ability to increase the effect of radiation in sterilizing neoplastic cells. The plan is to include patients who have carcinoma of the esophagus that appears to be clinically confined to the mediastinum and administer preoperative irradiation to all patients. Half of the patients will receive misonidazole, a hypoxic cell sensitizer, intravenously. Following completion of the radiotherapy, surgery will be performed and survival, freedom from lapse, and tumor viability within the pathologic specimen will all be evaluated. In addition, these patients, who are frequently cachetic, will serve as the basis for controlled studies of total parenteral nutrition.

214. A PHASE I CLINICAL TRIAL OF RADIATION SENSITIZERS AND A STUDY OF SOME OTHER THERAPEUTIC FACTORS

Thomas, G. M., Bush, R. S., Cummings, B. J., Dembo, A. J., Harwood, A. R., Hill, R. P., Rauth, A. M., Rider, W. D., Whitmore, G. F., Ontario Cancer Inst., Dept. of Radiation Oncology, *500 Sherbourne St., Toronto, Ontario*, M4X 1K9, Canada

OBJECTIVE: This is a phase I clinical and pharmacological investigation of two drugs, metronidazole and misonidazole. These drugs have potential use in the clinical setting as hypoxic cell radiation sensitizers. As such they may improve local control and cure with radiation of patients with carcinomas.

Our objective is to document and quantitate the types of acute toxicities associated with the administration of these drugs to patients receiving conventional daily fractionated radiation therapy to the pelvis in patients with carcinoma of the cervix and to the head and neck in patients with carcinomas of the head and neck.

APPROACH: Groups of patients are being studied at escalating levels of daily drug dosage. This will enable us to determine the maximum daily drug dosage which can be safely administered to such patients. It will also allow us to determine whether further trials to measure the therapeutic efficacy of these agents are justified.

Detailed pharmacokinetic studies using high pressure liquid chromatography are being performed to enable correlation of acute toxicities with plasma and urine drug levels.

215. CLINICAL STUDIES ON SENSITIZERS OF HYPOXIC TUMOR CELLS

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OBJECTIVE: To decrease the toxicity of these drugs by using methods that could alter the pharmacokinetics or metabolism, i.e., use of Dexamethasone (Decadron). To uncover potential toxicities that could occur when combining these drugs with other modalities. To predict the best timing of radiation treatment in different tumors. To assess whether there is improvement in patient survival when comparing this new approach with conventional treatment methods in patients harboring tumors of extremely poor prognosis. To improve the knowledge of the bioavailability of the drug and its pharmacokinetics when administered by different routes. To select tumors most likely to be benefited by these approaches.

APPROACH: The effectiveness of using radiosensitizers plus unconventional fractionated radiation will be compared to the best available conventional radiation using patients with glioblastomas. The comparative effectiveness of metronidazole versus misonidazole will also be assessed in this pilot clinical trial.

A modification of the neurotoxicity of these drugs will be assessed by the use of Decadron (Dexamethasone). The pharmacokinetics of misonidazole in solid tumor tissues will be assessed by performing multiple biopsies in 15 patients with different tumors. The drug will be administered p.o. and intravenously to compare bioavailability. Bone marrow toxicity to metronidazole and misonidazole will be assessed in humans by the colony forming units assay (CFU-C).

216. DEVELOPMENT OF ANTITUMOR AND RADIOSENSITIZING AGENTS

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A multidisciplinary effort is under way to design and synthesize (a) an antineoplastic agent effective against slow growing tumors, and (b) a radiosensitizing agent to selectively sensitize hypoxic tumor cells towards treatment with radiation. Triphenylphosphinegold complex of thymidine has been shown in our preliminary experiments to possess potent antineoplastic activity against P388 leukemia and B16 melanoma. Attempts will be made to delineate the biochemical mechanism(s) of action of this agent, and to design and synthesize a series of purine and pyrimidine analog complexes to increase the antineoplastic activity. Development of radiosensitizers has been undertaken to overcome the problem of radioresistance of hypoxic cells present in tumors toward ionizing radiation. An extensive structure activity relationship study is being carried out for nitroimidazole analogs in an attempt to reduce the CNS toxicity and increase therapeutic efficacy. To this end, a variety of 2-nitroimidazole nucleosides will be synthesized and tested for radiosensitization by in vitro and in vivo techniques.

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217. HYPERTHERMIC OXYGENATION AS A RADIATION SENSITIZER

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Preliminary physiological experiments demonstrated a rise in tumor TpO2 using short-term (10 min) localized mild hyperthermia (39-41 degrees C) both in animals and humans. The mechanism of this effect conceivably could be mediated through an increase in blood flow to the cancerous tissue. Associated effects on metabolism and intercellular pH remain to be determined. We propose to measure concomitantly TpO2, pH, local blood flow and tissue temperature using oxygen and pH ultramicroelectrodes (tip 1-5 microns), the local H(plus) generation method and microthermocouples respectively. Other functions such as blood pressure and body temperature will also be monitored. The objective is to establish the physiological mechanisms of observed rise in TpO2, as well as to document it in different tumors at several host organ sites in various species. The ratio between the increase in O2 tension in tumor and that in normal host tissue will also be studied.

Simultaneous radiobiological experiments will be performed to establish if this hyperthermic tumor oxygenation can be used as an adjuvant to radiation therapy. The tumor system in the initial studies will be a transplantable mouse mammary adenocarcinoma implanted into the upper hind limb of C3H mice. A holder has been designed which will hold 4 animals simultaneously with only the tumored portion of the legs exposed. For any given radiation dose the 4 animals will be treated as follows: 1) air, no heat; 2) air, heat; 3) oxygen, no heat; 4) oxygen, heat. Each dose point will consist of a total of 10-12 animals per experimental group (i.e. 40-48 animals per dose) for each of 10 doses. The simultaneous inclusion of the 3 control groups should provide necessary and sufficient controls. The animals will then be followed 3 times per week for both tumor and normal tissue response throughout a period of 120 days/animal (assuming cure).

Based on the data obtained subsequent experiments will be performed employing an in vivo/in vitro WAG rat rhabdomyosarcoma to determine the cellular basis for the survival data obtained.

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218. HYPOXIC CELL RADIOSENSITIZERS

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This is part of a broader project. A summary of this subproject is not available.

219. ORIGINS AND APPLICATIONS OF 5-FLUOROURACIL RADIOSENSITIZATION

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The objective of this research project is to determine the biochemical nature of the enhanced cytotoxicity found when tumor cells are exposed in tissue culture to a combination of 5-fluorouracil and x-rays. The research plan includes the addition of antimetabolites with defined modes of action coincident and separate from either x-ray or 5-FU exposure. By manipulating the various biochemical pathways for 5-FU activation and for its subsequent processing into primary antimetabolites (FdUMP and FUMP), it is anticipated that we can learn the mechanism by which this important anti-cancer drug influences radiation effect. The methodology involved is conventional biochemical approaches together with cell survival studies. Our initial studies have indicated that the drug Allopurinol can block the effectiveness of 5-FU in a variety of human tumor cells in

culture. These results would appear to suggest that the combination of 5-FU and x-rays together with Allopurinol is unlikely to be useful in cancer therapy. Currently under investigation are the coincident effects of hydroxyures and methotrexate. It is felt that the overall results of this program should yield useful information on combined 5-FU and drug x-ray scheduling in the context of human cancer clinical therapy.

220. PLASMATIC MEMBRANE AND ITS ROLE IN THE RADIORESISTANCE AND RADIOSENSITIVITY OF BREAST CANCER

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OBJECTIVE: To demonstrate that plasmatic membrane has a definite role in the radioresistance and radiosensitivity of breast cancer. The results will be used to decide which patients will and which will not respond to radiotherapy.

METHOD: We believe that the only way to determine the validity of the previous statement is by electron microscope study of specimens, before and after radiotherapy treatment.

PROGRESS: At the moment, we are studying four patients: a) Breast cancer 'with membrane,' b) breast cancer 'with a few cells with membrane,' c) breast cancer 'with a lot of cells with membrane,' and d) breast cancer 'without membrane.'

221. RADIATION SENSITIZER NEUROTOXICITY

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No summary has been provided to the Smithsonian Science Information Exchange.

222. RADIOSENSITIVITY STUDIES IN LYMPHOPROLIFERATIVE DISORDERS

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For the last two years the ICRF technique for determining in vitro radiosensitivity of lymphocytes has been established in the Department of Hematology at St. Thomas's Hospital. During this time a total of 100 radiosensitivity studies have been made in 44 patients. Thirty-six of these patients have been cases of classical chronic lymphocytic leukemia (CLL) but a small number of patients with prolymphocytic leukemia, leukemic reticulo endotheliosis, T cell leukemia and non-Hodgkin's lymphoma have been included. Simultaneous measurement of B and T cell markers, mouse-rosetting and colchicine sensitivity have been made. Initial results in untreated patients show that virtually all patients with typical B cell type CLL have populations that have in vitro sensitivity equal to and even greater than populations from normal control individuals. In patients treated with low dose splenic irradiation there has invariably been an immediate fall in peripheral lymphocyte count but the number of CLL patients with in vitro radio-resistant lymphocytes is so far, too small to establish whether the in vitro results predict in vivo response. Data are now accumulating over long term serial studies which are designed to explore the following areas: the value of in vitro sensitivity in predicting long term clinical haematological response to serial low dose radiation; the possible selective elimination by low dose therapy of abnormal lymphocyte population - with sparing of normal, particularly T cell, populations; the development of in vitro radio resistance following either chemotherapy or low dose radiotherapy; the correlation, if any, between in vitro radiosensitivity and other clinical, hematological and cell characteristics.

223. DETERMINATION OF RADIOSENSITIVITY AND FRACTIONATION EFFECTS IN HUMAN CERVICAL CARCINOMAS

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OBJECTIVES: A better understanding of the radiobiological effects of irradiation on growth patterns of both malignant tumors (human cervical tumors) and normal tissue. Determination of the relation between the prognosis and the parameters found (the ploidy level of the tumor and the histogram of the DNA distribution in the tissue resulting in percentages of cells in G0 plus G1-, S-, and G2 plus M-phase of the cell cycle). Gaining insight into factors influencing the radiosensitivity as expressed by the inhibition of cell cycle progression in the G2-phase of the cell cycle. The obtained knowledge might result in individually tailored fractionation schemes of the cesium-137 applications (the second application at the moment of maximal accumulation of cells in G2).

APPROACH: From patients with cervical carcinoma, biopsies are taken before and 14 days after irradiation with a cesium-137 application (about 4000 rads). Cell suspensions are prepared and run through a flow cytometer. The obtained DNA distribution results in the ploidy level of the tumors and the percentage of cells in the S-phase and in the G2 plus M-phase of the cell cycle. At the moment of the second biopsy the irradiation-induced G2-block may or may not be still present. The pattern of accumulation of cells in the G2-phase after irradiation will be determined more extensively in human cervical tumors transplanted in nude athymic mice. The DNA-histograms are analyzed using an iterative computer program developed by P.M. van der Linden. Cell populations blocked at some point in the cell cycle can be analyzed by this program.

PROGRESS: Progress on patient material is good (85 patients examined). The work with nude mice progresses slowly, because it is very difficult to cause human cervical tumors to grow in nude mice. More than 20 human cervical tumors have been transplanted and only one has grown. A human cervical tumor cell line (ME180) has been successfully transplanted and other human cervical tumor cell lines will also be tested. The parameters found with flow cytometry will be examined in correlation with the prognosis using a computer.

224. RESEARCH INTO VARIATIONS IN HUMAN TISSUE RADIOSENSITIVITY ACCORDING TO CIRCADIAN OSCILLATIONS

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Circadian oscillations of the cellular proliferation have been observed in several proliferating tissues and in non-proliferating tissues induced to regenerate. The existence of such oscillations has been confirmed in some tumors of laboratory animals and data also exist on skin tumors of man. As the cellular radiosensitivity is known to be cycle dependent, timing of irradiation can be supposed to modify the cellular response to irradiation. Research carried out at the Radiobiology Laboratory of this Institute demonstrates that the intestinal damage in rats varies to a considerable degree depending on the timing of irradiation. Based on this assumption, this project has been devised with the two follow-up goals: 1) to evaluate the existence of different degrees of the radioresponse depending on the time of irradiation in human tissues as well, and 2) to evaluate the possibility of using this phenomenon to increase the therapeutic ratio in radiotherapy of tumors.

The clinical part of the project has now begun. Patients selected for the project are mainly those affected by cervical cancer, which is easily observable and available for multiple biopsies.

The project includes the clinical observation of the skin and mucosal reaction and of the neoplastic regression, the determination of some biochemical indicators of the radiation injury, and the in vitro incorporation of 3H-thymidine.

Patients have been divided into two groups according to the time of irradiation: Following the experimental observations on the rats, the irradiation has been performed between 7 and 9 a.m. in the first group and between 6 and 8 p.m. in the second group.

225. CHEMICAL MECHANISMS OF RADIATION SENSITIZATION BY OXYGEN

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This is part of a broader project. A summary of this subproject is not available.

III. RADIOTHERAPY OF SPECIFIC BODY SITES

A. RADIOTHERAPY OF HEMATOLOGIC DISORDERS

226. THERAPY OF LYMPHOMAS, ACUTE ADULT NON-LYMPHOCYTIC LEUKEMIA AND HEPATOCELLULAR CARCINOMA

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OBJECTIVE: To determine the efficacy of combined chemotherapy and/or radiotherapy in Chinese patients with malignant lymphomas, acute adult non-lymphocytic leukemia and hepatocellular carcinoma.

APPROACH: (a) To compare mainly COPP, MOPP, doxorubicin (Adriamycin)-COP, CVP regimes in treatment of lymphomas. Classification: Rappaport, and more recently with T and B cell markers. Staging: Ann Arbor. (b) To use, in adult patients with acute non-lymphocytic leukemia, cytosine arabinoside (ara-C)/doxorubicin i.e. 5:2 scheme for induction; ara-C/thioguanine for remission-induction and azacytidine for refractory cases. (c) Doxorubicin has been used in 19 patients with inoperable hepatocellular carcinoma. In 10, three or more doses were administered and objective evidence of tumor regression was seen in 3. Survival was statistically improved when compared with controls matched for sex, age, duration of symptoms and tumor staging.

PROGRESS: (a) Some results have been reported in Abstracts, XV, International Congress of Haematology, p. 205, Kyoto, 1976. (c) Preliminary data were presented at the Third Asian Cancer Conference in Manila, September 26-30, 1977.

227. RADIATION-RELATED THYROID DYSFUNCTION IN HODGKIN'S DISEASE

Schimpff, S. C., Wiernik, P. H., Salvatore, P., Wiswell, J. G., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Section of Infection Research, *Baltimore, Maryland*, 21201, United States of America

Late complications in the treatment of Hodgkin's disease with radiation therapy are increasingly being recognized. Thyroid dysfunction following irradiation is one such complication which has not been widely recognized, probably because of the subtle clinical nature of minor thyroid hormone imbalance. In addition, it has long been thought that the thyroid was relatively resistant to radiation therapy. Two hundred thirty-two patients with Hodgkin's disease followed at the BCRP have been evaluated for post-therapy thyroid dysfunction. Forty-one percent of those with mantle radiation therapy had an elevated TSH, but normal T4; however, an additional 25% had an elevated TSH plus a depressed T4. Thus, 66% of 169 patients had evidence of thyroid dysfunction following mantle radiation therapy. Since thyroid hormone replacement is simple, inexpensive and usually without major side effects if properly monitored, it is reasonable in light of the foregoing to place all patients with an elevated TSH on thyroid replacement therapy regardless of whether or not they are chemically hypothyroid.

BIBLIOGRAPHIC REFERENCES: Schimpff, S.C.: Carcinoma of the thyroid. In Aisner, J., and Chang, P. (Eds.): Advances in Cancer Treatment Research. The Netherlands, Martinus Nijhoff, Publ., 1980, pp. 88-102. Schimpff, S.C.: Hormonally active tumors. In Lichtman, M.A., and Wiernik, P.H. (Eds.): The Science and Practice of Clinical Medicine. New York, Grune and Stratton, 1980 (in press).

228. RADIOTHERAPY, CHEMOTHERAPY OR COMBINED MODALITY TREATMENT FOR EARLY HODGKIN'S DISEASE

Wiernik, P. H., Young, R. C., Glatstein, E., Slawson, R., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Oncology Branch, *Baltimore, Maryland*, 21201, United States of America

The summary for this project is under entry no. 148.

229. RADIOTHERAPY IN LYMPHOHEMATOPOIETIC TRANSPLANTATION (HUMAN, RATS)

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This is part of a broader project. A summary of this subproject is not available.

230. THYMIC RADIATION IN CHRONIC LYMPHOCYTIC LEUKEMIA (HUMAN)

Carpenter, J. T., University of Alabama in Birmingham, School of Medicine, Dept. of Medicine, *1919 7th Ave. S., Birmingham, Alabama*, 35233, United States of America

This is part of a broader project. A summary of this subproject is not available.

231. TOTAL BONE MARROW RADIATION IN MYELOMA

Coleman, M., Wolf, D., Nisce, L., Cornell University, Medical Center, New York Hospital, Division of Hematology & Oncology, *1300 York Ave., New York, New York*, 10021, United States of America

OBJECTIVE: To determine if radiation given to marrow-bearing areas will augment the response to chemotherapy.

APPROACH: Following induction of response, myeloma patients are given 2000 rads to the major bone marrow areas using a modification of the 3 and 2 technique used in Hodgkin's disease. Two separate courses of 1000 rads each are given sequentially, followed by betatron therapy to ribs and skull radiation.

PROGRESS: Nine patients have been treated. Hematologic toxicity is the main side effect. Responses in the monoclonal spike have been obtained.

232. PHASE I-II STUDY OF TOTAL BODY IRRADIATION IN PATIENTS WITH MULTIPLE MYELOMA FAILING SYSTEMIC CHEMOTHERAPY

Bunn, P. A., Schechter, G., Lichter, A. S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *50 Irving St. N.W., Washington, District of Columbia*, 20422, United States of America

Multiple myeloma is rarely 'cured' by chemotherapy although clinical remissions are frequent and median survival is lengthening. When patients fail primary drug therapy, second line treatment produces few responses and those are of short duration. Plasma cells are sensitive to irradiation and local deposits of plasma cells (plasmacytomas) can be controlled with x-ray. Total body irradiation may produce significant killing of myeloma cells even if the radiation is administered in low doses such as is given in advanced stage lymphoma. We propose to treat patients who have failed standard chemotherapy for multiple myeloma with total body irradiation in order to assess the efficacy of this type of therapy.

233. TOTAL BODY IRRADIATION FOR BONE MARROW TRANSPLANT

Kim, T. M., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Therapeutic Radiology, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

This is part of a broader project. A summary of this subproject is not available.

234. PHYSICAL ASPECTS OF TOTAL SKIN ELECTRON IRRADIATION

Padikal, T. N., Glatstein, E., Fraass, B. A., Roberson, P. L., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Radiation Physics & Computer Automation Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The Mev XII linear accelerator has been modified for use in total skin electron irradiation, such as mycosis fungoides. Dosimetric features have been ascertained and treatment of mycosis fungoides patients has been initiated.

B. RADIOTHERAPY OF ALIMENTARY AND GENITOURINARY DISORDERS

235. RELATION BETWEEN PROLIFERATIVE ACTIVITY AND CLINICAL RESPONSE OF ORAL CARCINOMAS TO RADIOTHERAPY

Molinari, R., Silvestrini, R., Chiesa, F., Costa, A., Costa, L., Volterrani, F., Istituto Nazionale per lo Studio e la Cura dei Tumori, Dept. of Clinical Oncology C, *1 Via G Venezian, 20133 Milan, Italy*

OBJECTIVE: To study the correlation between kinetic and clinicopathological characteristics of primary tumor; to rationalize the choice and sequence of different clinical treatments on the basis of the proliferative changes induced by radiotherapy.

APPROACH: The study is carried out on untreated patients. Tumor biopsy specimens are cut into small fragments and incubated for 1 hour at 37 degrees C with 3H-thymidine. Autoradiographs of histological sections are performed with stripping film techniques. The kinetic determination is carried out before and after 1000 r (200 r/day for 5 days, using 60Co unit).

PROGRESS: The proliferative activity of primary tumor ranged from 0.01% to 27% of labeling index, and a negative correlation was observed between proliferative activity of primary cancer and age of patients. The proliferative activity was medially lower in tumors without clinically evident metastasis in comparison with tumors with involved nodes.

236. RADIOTHERAPY OF CANCER OF THE ESOPHAGUS - PREOPERATIVE RADIOTHERAPY

Guerra, G., Gaitan, A., Valbuena, J. V., Instituto Nacional de Cancerologia, Seccion de Radioterapia, *Apartado Aereo #17.158, Calle 1 No. 9-85, Bogota, DE, Colombia*

OBJECTIVE: a) To unify the criteria of diagnostic and therapeutic procedure in cancer of epithelial origin, in accordance with the TNM classification and location of the tumor. b) To evaluate morbidity and mortality of treatment. c) To evaluate the reliability of the available diagnostic methods and their usefulness in the TNM classification. d) To evaluate the use of preoperative radiotherapy in middle or lower esophageal cancer

MATERIAL: Patients with adenocarcinoma or squamocellular carcinoma of the esophagus, excluding a) patients previously tested outside the Instituto Nacional de Cancerologia, b) patients in whom the risk of surgery prohibits radical surgery which would otherwise be the preferred treatment, and c) patients with advanced tumors (T2, T3, T4, N2 or M plus).

METHOD: Preoperative supervoltage radiotherapy, 2,000 rads over one week (5 fractions). Radical surgery, removal of lymph nodes from the lower curvature of the stomach, the paraortic region and celiac trunk, followed by restoration of function. (Translated)

237. A RANDOMIZED PROSPECTIVE STUDY OF PREOPERATIVE RADIATION THERAPY IN CARCINOMA OF THE STOMACH AND DISTAL ESOPHAGUS

Wilson, S. E., Petrovich, Z., Guth, P. H., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Surgical Service, *Wilshire & Sawtelle Blvds., Room 209, Los Angeles, California,* 90073, United States of America

This randomized study is evaluating the effectiveness of pre-operative radiation therapy for patients with both adenocarcinoma and squamous cell carcinoma of the distal esophagus and proximal half of the stomach. Radiation therapy consists of 4,000 rads in fractionated doses over 4 to 5 weeks followed by the surgery.

In the first twelve months five patients have been included in the study on Preoperative Radiation for Adenocarcinoma of the Distal Esophagus and Proximal Stomach. Two patients were operated upon and surgery carried out primarily. One surived six months and the other survived nine months. In one patient exploratory surgery was carried out but resection was not possible. In a fourth patient preoperative radiation was given but on exploration the patient was found to have inoperable disease. The last patient underwent preoperative radiation of 4,000 rads; exploration was carried out and resection performed. However, the patient died postoperatively of a pneumonic process. Accrual of patients for treatment of carcinoma of the proximal stomach and distal esophagus is slow since the incidence of this disease is low. No conclusions can be drawn from this small sample of patients.

238. ACUTE AND CHRONIC EFFECTS OF RADIOTHERAPY ON ESOPHAGUS

Northway, M. G., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Diagnostic Radiology, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas,* 77030, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

239. THERAPY OF PATIENTS WITH GASTRIC CARCINOMA

Holyoke, E. D., State Dept. of Health, *Empire State Plaza, Tower Bldg., Albany, New York,* 12237, United States of America

The employment of multiple therapeutic modalities in treatment of resectable, unresectable and disseminated gastric carcinoma to increase the rate of cure, survival and palliation is undertaken. Since chemotherapy and radiation therapy can destroy the disseminated cancer cells and local microscopic foci of tumor, both modalities are used singly and in combination in treatment. These studies continue.

240. THERAPY OF PATIENTS WITH GASTRIC CARCINOMA

Spiro, H. M., Yale University, School of Medicine, Dept. of Internal Medicine, *333 Cedar St., New Haven, Connecticut,* 06510, United States of America

This project proposes to improve the palliation and survival of patients with gastric carcinoma by randomized, controlled, stratified treatment programs involving chemotherapy and radiation therapy. The objectives and scope of the renewal period have not changed significantly from the prior reporting period.

241. POSTOPERATIVE RADIOTHERAPY IN PATIENTS WITH CANCER OF THE RECTUM AND SIGMOID COLON, DUKES' B AND C (A PROSPECTIVE, RANDOMIZED STUDY)

Kronborg, O., Balslev, I., Bertelsen, K., Bone, J., Hage, E., Hostrup, H., Jacobsen, N. O., Overgaard, J., Pedersen, M., Sell, A., Sorensen, F. H., Teglbjaerg, P. S., Odense Hospital, Dep. of Surgical Gastroentology, *DK5000 Odense, Denmark*

OBJECTIVES: Does postoperative radiotherapy influence crude 5-year survival? Does postoperative radiotherapy alter the frequency and time of local recurrence? What are the complications after postoperative radiotherapy and how often do they occur? Has CEA any prognostic value?

APPROACH: 550 patients with rectosigmoid cancer (Dukes' B and C) are allocated to surgery alone or surgery plus postoperative radiotherapy. Five surgical departments and 3 radiotherapy departments are involved. The patients are selected by 7 criteria of exclusion. Follow-up is performed 6 months, 1, 2, 3, 4 and 5 years after surgery. CEA is measured before and after surgery and at the follow-up examinations, but the results will not be known before the study is finished. The study began in September 1979 and is planned for completion in 1988.

242. TREATMENT OF COLORECTAL CANCER BY POSTOPERATIVE RADIOTHERAPY

Ghossein, N. A., Alpert, S., Rubinstein, A., Escher, G. C., Kadish, A. S., Kaplan, B. H., Turner, S. S., Ragins, H., Yeshiva University, Bronx Campus, Albert Einstein School of Medicine, Dept. of Radiology, *1300 Morris Park Ave., Bronx, New York,* 10461, United States of America

As of December 1979, 153 patients have received elective postoperative radiotherapy, with moderate doses, for a locally advanced colorectal cancer (Stage B2, C1, C2). Ninety had rectosigmoid cancer and 55 a colonic lesion. One hundred twenty-five patients had a minimum follow-up of twelve months. The absolute survival, with a mean follow-up of thirty months, of patients with B2 and C1 lesions is about 70%. That of C2 is 55%. The absolute survival at 24 and 36 months for the entire 125 patients is 69% and 53% respectively. Eighty-three percent and seventy-nine percent of the patients are recurrence free for the same period of time. Thirty-one patients had residual disease remaining following the surgical resection. Twenty (65%) are locally controlled. Radiation complications occurred

in six of the 125 patients (6%). Only one patient (0.8%) had a fatal complication.

We are continuing to study the effect of large-field irradiation on the immune status of these patients. So far, we have documented the suppression of mitogenic response from non-specific mitogens and the decrease in the number of peripheral T-lymphocytes. Also, interestingly, there is an increase in the number of activated monocytes following radiotherapy which may be due to the release of immune complexes.

From our data, it appears that postoperative radiotherapy should be given routinely, following the surgical resection of a locally advanced colorectal cancer.

243. ADJUVANT RADIATION THERAPY FOR OPERABLE RECTAL CARCINOMA (HUMAN)

Mohuiddin, M., Thomas Jefferson University, Jefferson Medical College, Dept. of Radiation Therapy & Nuclear Medicine, *1025 Walnut St., Philadelphia, Pennsylvania,* 19107, United States of America

This is part of a broader project. A summary of this subproject is not available.

244. PROSTATIC CARCINOMA - COOPERATIVE STUDY OF RADIOTHERAPY VS. SURGERY OR DELAYED HORMONAL THERAPY

Paulson, D. F., Stefani, S. S., Olsson, C. A., Ucmakli, A., Ciavarra, V., Roswit, B., Nelson, R. P., Wallace, K., Clark, S. S., Lee, N., Dees, J., Miller, L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Uro-Oncology Research Group, *508 Fulton St., Durham, North Carolina,* 27705, United States of America

The purpose of this project is to determine the relative merits of initial radiotherapy versus radical prostatectomy for patients in whom prostatic carcinoma is confined to the prostate and to determine the relative merits of initial radiotherapy versus delayed hormonal therapy in those in whom it is more widespread. Patients admitted to participating hospitals who are suspected of having prostatic carcinoma undego a complete history and physical, prostatic biopsy, lymphangiograms, bone x-rays, serum acid phosphatase, bone scan and staging pelvic lymphadenectomy where indicated to permit staging of disease to one of seven categories related to extent and spread. Radiation therapy to be used will be 6000 R per 36 days to 7000 R per 50 days, central prostate dose, using megavoltage. Lymph node extension is identified, extended periaortic irradiation will be given.

As of this time, the patients are under follow-up. No new patients are now being randomized to treatment. Three hundred forty-six patients were randomized to receive a specific treatment and are presently under follow-up. No specific adverse effects to any of the treatments have been identified and no specific benefits to any of the treatments has been established.

245. COOPERATIVE STUDY OF RADIOTHERAPY VERSUS SURGERY OR DELAYED HORMONAL THERAPY IN TREATMENT OF PROSTATIC CARCINOMA

Ciavarra, V. A., Roswit, B., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Urology Section, *130 W. Kingsbridge Rd., Bronx, New York,* 10468, United States of America

The study has not been in progress for a sufficient period of time to permit meaningful comparisons between the various forms of treatment being studied. Results thus far do reveal the value of diagnostic studies such as bone scans, lymphangiography, and lymph node biopsies in assessing more accurately the clinical stage of disease in patients with prostatic cancer.

246. GONADAL RADIATION AND SPERMATOGENESIS IN CANCER PATIENTS

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This is part of a broader project. A summary of this subproject is not available.

247. TREATMENT OF CERVICO-UTERINE CANCER WITH INTRAUTERINE HIGH-YIELD RADIATION

Garcia Sainz, G., Armendariz, C., Vazquez Curiel, A., Rodriguez, C., Instituto Mexicano del Seguro Social, *Av. Cuauhtemoc No. 330, c/o Hsp. Oncol.-Ctr. Med. Nac., Mexico City 7, Distrito Fed., Mexico*

OBJECTIVES: To evaluate therapeutic results and tolerance to treatment of cervicouterine carcinoma with the Cathetron, in comparison with results obtained using the established treatment of the Hospital de Oncologia which utilizes radium combined with external radiotherapy. To determine whether the new method may be substituted for the old one in light of such practical advantages as greater radiological protection of personnel, treatment on an out-patient basis and consequent savings in hospital days, and strict adherence to the treatment schedule.

In this controlled clinical trial the null hypothesis will be evaluated since, by definition, the new treatment is designed to satisfy conditions of isoeffectivity. If the null hypothesis is not rejected by this study it may be concluded that the new treatment is equivalent to the old in therapeutic effect and clinicopathologic tolerance. In that case it may be the treatment of choice because of the advantages in radiologic protection and savings in hospital days.

Patients with epidermoid cervico-uterine carcinoma will be accepted to the study with the following exceptions: a) Patients who have had prior therapy. b) Patients over 70 years of age. c) Pregnant patients. d) Patients without an IMSS courtesy card. e) Patients who do not meet our criteria.

Patients who are accepted are randomized with stratification by clinical stage and assigned to treatment utilizing the Cathetron or the Hospital de Oncologia technique. Randomization is performed using tables with random numbers as published by Hill. A minimum of 300 patients will be assigned to each treatment in order to include at least 60 patients from each clinical stage in the study.

The following parameters will be analyzed: a) Interval free of tumoral activity based on initiation of treatment. b) Survival free of tumoral activity. c) Survival with tumoral activity. d) Proctitis. e) Cystitis. f) Leukopenia. g) Bone necrosis. (Translated)

248. THE CATHETRON IN THE TREATMENT OF CANCER OF THE UTERUS

Taina, E. J., University Central Hospital of Turku, Depts. of Obstetrics & Gynaecology & Radiotherapy, *Pentti Kilkku, Naistenklin. TYKS, SF20520 Turku 52, Finland*

OBJECTIVE: Radium has been used for decades in the treatment of cancer of the uterus. There are, however, certain difficulties in the dosimetry of the treatment and in protecting the staff from the radiation. These difficulties are greatly reduced by using the Cathetron afterloading device in the treatment. Cathetron treatment is new and its effect has not been thoroughly analyzed yet.

APPROACH: This study will compare radium and Cathetron treatments with each other. The material for the study derives from the patients treated with either radium or the Cathetron in 1969-76. The study is divided into two parts: a clinical and a clinical-biophysical one.

PROGRESS: The material will be analyzed to determine the patients' survival, complications and operability after the treatment. The study also aims to solve the problems of treatment planning consisting of fractionation, dosage and treatment time. Comparison between TDF and CRE will also be made. The results of the present study will hopefully be available in 1981.

249. RADIOTHERAPY OF ADVANCED CANCER OF THE UTERINE CERVIX

Noguera, N., Galtan, A., Instituto Nacional de Cancerologia, Seccion de Radioterapia, *Apartado Aereo #17.158, Calle 1 No. 9-85, Bogota, DE, Colombia*

OBJECTIVE: To determine the effectiveness of high doses of radiation administered over a short period of time as palliative treatment in advanced carcinoma of the uterine cervix.

MATERIAL: Patients with adenocarcinoma or squamocellular carcinoma of the uterine cervix in advanced stage III, with 'frozen pelvis' and IV-A for bladder invasion, without fistula.

METHOD: Supervoltage radiotherapy, 3,000 rads in 2 weeks (10 fractions). (Translated)

250. RADIATION RESPONSE AND UTERINE CANCER (HUMAN)

Rubin, P., University of Rochester, School of Medicine & Dentistry, Dept. of Medicine/Radiology/Surgery, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

This is part of a broader project. A summary of this subproject is not available.

251. EXTENSION OF RADIOTHERAPY RESEARCH - FEMALE GENITAL TRACT

Fletcher, G. H., Almond, P. R., Tapley, N. D., Withers, H. R., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Radiotherapy, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

The current and planned programs are in four areas: a) basic and applied research projects, b) clinical applications of modified and newly standardized techniques and treatment modalities, c) development and initiation of methods of data collection and analysis, and d) utilization of materials, facilities, and skills for teaching and training pre- and postgraduate students, resident physicians, and community physicians and other personnel.

252. ADJUVANT RADIATION THERAPY FOR OPERABLE BLADDER CANCER (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

C. RADIOTHERAPY OF OTHER BODY SITES

253. EARLY BREAST CANCER - TRIAL COMPARING LOCAL EXCISION AND AXILLARY DISSECTION AND RADOTHERAPY WITH RADICAL MASTECTOMY

Hayward, J. L., Millis, R., Winter, P. J., Tong, D., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Pilot studies have now begun to test the feasibility of undertaking a clinical trial on the use of local excision with axillary dissection, followed by internal and external irradiation, in the treatment of patients with early breast cancer. Selected patients with T1,2NO,1MO tumors, in whom the diagnosis of breast cancer has been made by Tru-Cut biopsy, are having their tumor excised locally and an axillary dissection carried out. At the same time, metal wires are being inserted through the tumor bed and plastic tubes pulled through and left in situ. Some three days later these tubes are loaded with iridium. After an appropriate dose has been administered the wires are removed, and subsequently the breast and internal mammary chain are being subjected to external irradiation. This method of management has the advantage that it gives effective local treatment of the tumor, with accurate axillary staging, but allows the patient's breast to be retained.

If the pilot studies are successful a clinical trial will be undertaken to compare this method of management with modified radical mastectomy.

254. EFFECTS OF RADIATION THERAPY ON CELLULAR AND HUMORAL IMMUNITY OF PATIENTS WITH BRONCHOGENIC CARCINOMA (ABBREV)

Eells, R., McLaren, J., Olkowski, Z., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Radiology Service, *1670 Clairmont Rd., Decatur, Georgia*, 30033, United States of America

Accession of new patients has been closed, with 61 evaluable cases. The group randomized to adjuvant BCG/levamisole and the group receiving radiotherapy alone were reasonably comparable as to age, sex, site and stage. At entry, 82% showed impaired immunocompetence (as compared to age-matched controls without cancer). To date, there have been no significant differences between the immunotherapy and radiation only groups with respect to tumor control, disease-free interval, or survival curves. There were some variations between the two groups in the immunologic parameters, but these were not statistically significant. In vitro test results for all patients were as follows: T cell absolute numbers decreased at entry, with further fall at end of radiation, but recovery occurring at 8 weeks. T cell percentages decreased at entry, with no further changes after radiation or during follow-up to 40 weeks; B cell absolute numbers decreased at end of radiation, but with subsequent recovery maintained through 40 weeks; B cell percentages showed no significant alterations; blastogenesis (with PHA and PWM) decreased at entry, with further fall after radiation, and partial recovery during follow-up through 28 weeks; sialic acid levels elevated, without further change at end of the radiation or on later follow-up. Lymphocyte cytotoxicity showed no apparent radiation effects, but has been discontinued because of complexity and variability of the results. Median survival had not been reached at last review. Monitoring of patients continues with periodic immunologic profiles. Further correlation of test results with clinical course and outcome will be made.

255. HALF-BODY IRRADIATION IN EXTENSIVE OAT CELL CARCINOMA

Qasim, M. M., The, S. K., Boulis Wassif, S., Seldenrath, J. J., Treurniet, R. E., Rotterdamsch Radiotherapeutisch Instituut, Dept. of Radiotherapy, *Groene Hilledijk 301, Box 5201, 3075 EA Rotterdam, Netherlands*

OBJECTIVE: A prospective randomized trial for extensive oat cell bronchus carcinoma comparing aggressive chemotherapy versus half-body radiotherapy and adjuvant chemotherapy.

APPROACH: Patients are randomized into two arms: 1) Chemotherapy with Adriamycin, Cyclophosphamide and Oncovin 6 cycles every 3 weeks, followed by maintenance chemotherapy. 2) Radiotherapy with 1 x 7 Gy upper half-body irradiation, one-week interval, followed by 2 cycles of Adriamycin, Cyclophosphamide and Oncovin every 3 weeks. Four- to six-week interval for hematological recovery followed by 1 x 7 Gy lower half-body irradiation.

PROGRESS: Study has just started. Results will be published later.

256. MEDIASTINAL IRRADIATION FOR CARCINOMA OF THE LUNG

Dillon, M. L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *Leestown Pike, Lexington, Kentucky*, 40507, United States of America

A discriminative analysis is being done to determine whether factors other than radiation treatment contribute to the survival of patients operated on for carcinoma of the lung.

Since 1975, we have entered 58 patients into the study with 26 randomized to treatment and 32 to the non-treatment group. Of the patients who received postoperative mediastinal irradiation, 12 have died. Eight patients from the group that did not receive postoperative irradiation have died.

In terms of survival, at this point, there seems to be little benefit from the use of postoperative mediastinal irradiation therapy, but differences may become apparent with longer follow-up since 24 of these patients entered the study within the last 2 years. There is a difference in bronchial recurrence of 8.3% compared to 23.5% in the group undergoing surgery only. Distant metastases were the initial site of relapse in 5 of 24 patients given postoperative irradiation, but in only 1 of 34 patients who underwent only surgery.

257. RADIATION THERAPY FOR INOPERABLE LUNG CANCER (HUMAN)

Mohuiddin, M., Thomas Jefferson University, Jefferson Medical College, Dept. of Radiation Therapy & Nuclear Medicine, *1025 Walnut St., Philadelphia, Pennsylvania*, 19107, United States of America

This is part of a broader project. A summary of this subproject is not available.

258. INTRAOPERATIVE RADIATION THERAPY FOR PANCREAS CANCER

Goldson, A. L., Ashayeri, E., Roux, V. J., Cornwell, E. E., Rayford, L. L., Chisholm, R., Howard University, School of Medicine, Dept. of Radiation Therapy, *2400 6th St. N.W., Washington, District of Columbia*, 20001, United States of America

Intraoperative radiotherapy (IOR) of 15 patients with advanced pancreas cancer using 9-15 MeV electron beams of a linear accelerator showed that IOR is a practical and safe procedure with demonstrable major tumoricidal effect in all five patients who came to autopsy. Although 13 of the 15 patients have died, none of the five autopsied patients succumbed to a local recurrence in the treated area. To avoid complications with IOR the radiation doses should be kept below 3000 rads for small volumes and below 2000 rads for large volumes. If these limits are respected and the intestines, except the involved duodenum, are kept out of the radiation beam, the risk and inconvenience of adding IOR to the usual abdominal exploration with biopsy and bypass is negligible. If, however, abdominal exploration and bypass have already been performed, a second operation for the purpose of IOR is advised only if the primary is small and no metastases are demonstrated.

259. THERAPY OF PATIENTS WITH PANCREATIC CARCINOMA

Kaiser, M. H., University of Miami, School of Medicine, Dept. of Medicine, *1400 N.W. 10th Ave., Box 520875, Coral Gables, Florida*, 33152, United States of America

Independently and not as an agent of the Government, The Contractor shall exert its best efforts to conduct studies and to carry out clinically indicated modes of therapy as these involve patients with pancreatic carcinoma. The therapeutic regimens, as well as the ensuing studies, will be performed on at least twenty-five patients per year, each of whom has a microscopically confirmed diagnosis of pancreatic carcinoma; and whose primary neoplasm has been staged and further characterized according to histological type. The studies will be conducted in accordance with the following protocols: Combined 5-Fluorouracil and Supervoltage Radiation Therapy as an Adjuvant to Surgical Treatment of Pancreatic Carcinoma; and a Controlled Evaluation of High Dose (6000R) Radiation Therapy, High Dose Radiation Therapy plus 5-FU, and Medium Dose (4000R) plus 5-FU in the Treatment of Locally Unresectable Carcinoma of the Pancreas.

260. THERAPY OF PATIENTS WITH PANCREATIC CARCINOMA

Spiro, H. M., Yale University, School of Medicine, Dept. of Internal Medicine, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

This project proposes to improve the palliation and survival of patients with pancreatic carcinoma by randomized, controlled, stratified treatment programs involving chemotherapy and radiation therapy. The objectives and scope of the renewal period have not changed significantly from the prior reporting.

261. THERAPY OF PATIENTS WITH PANCREATIC CARCINOMA

Moertel, C. G., Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota*, 55901, United States of America

Independently and not as an agent of the Government, the Contractor shall exert its best efforts to conduct studies and to carry out clinically indicated modes of therapy as these involve patients with pancreatic carcinoma. The therapetic regimens, as well as the ensuing studies, will be performed on at least twenty-five (25) patients per year, each of whom has a microscopically confirmed diagnosis of pancreatic carcinoma, and whose primary neoplasm has been staged and further characterized according to histological type. The studies will be conducted in accordance with the following protocols: Combined 5-fluorouracil and supervoltage radiation therapy as an adjuvant to surgical treatment of pancreatic carcinoma; and a controlled evaluation of high dose (6000R) radiation therapy, high dose radiation plus 5-FU, and medium dose (4000R) plus 5-FU in the treatment of locally unresectable carcinoma of the pancreas.

262. COMBINED INTERSTITIAL AND HIGH DOSE EXTERNAL BEAM THERAPY FOR PANCREAS CANCER

Dobelbower, R. R., Thomas Jefferson University, Jefferson Medical College, Dept. of Radiation Therapy & Nuclear Medicine, *1025 Walnut St., Philadelphia, Pennsylvania*, 19107, United States of America

This is part of a broader project. A summary of this subproject is not available.

263. EVALUATION OF THE ROLE OF RADIOTHERAPY IN PRIMARY LIVER CANCER

Nair, T. C., Kumar, T. V., Ramachandran, P. V., Medical College Hospitals, Dept. of Radiotherapy, *Chevayoor Kerala, Calcutta 700073, West Bengal, India*

OBJECTIVE: To evaluate the role of radiotherapy in the management of hepatic malignancies.

APPROACH: The number of primary liver cancer patients attending the department is about 100 per year. These cases are divided into two groups: one group is treated with chemotherapy and the other group is evaluated regarding nature and duration of survival, and liver function and complications are assessed.

264. METRONIDAZOLE AND LARGE FRACTION BRAIN IRRADIATION FOR GLIOBLASTOMA

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Patients with glioblastoma multiforme are currently treated with resection followed by conventional radiotherapy with an extremely low incidence of tumor control. There is radiobiological evidence that larger individual fractions of irradiation (e.g 600 rads) might be more effective in killing glioblastoma cells Since the electron affinic compound metronidazole has been shown to have in vitro, in vivo and clinical activity in sensitizing hypoxic tumor cells to irradiation, it would be reasonable to study the use of this drug in combination with large individual fractions of irradiation for the treatment of patients with glioblastoma multiforme. A pilot study is indicated to better define the toxicity to normal central nervous system tissues of such combined therapy and to determine the incidence of local control of this tumor and survival using this treatment.

265. STUDY OF THE TREATMENT OF MALIGNANT GLIOMA OF THE BRAIN

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The Brain Tumor Study Group is the National Cancer Institute's prime source of treatment testing for compounds and approaches which have a high potential for the treatment of brain cancer.

Phase II BTSG protocols are designed to admit patients with brain tumors not eligible for the Phase III study in order to determine the comparative value of a given mode of therapy, the problems in utilizing such therapy, and the toxicity which might be reasonably anticipated. The basic design is one of a continuous flow protocol in which specific agents will be replaced in the study as their comparative value is determined. The protocol will allow for a more careful and rapid selection of potential agents for Phase III studies.

The current randomized Phase III studies are: Surgery followed by Radiotherapy and BCNU vs. Radiotherapy and BCNU followed by Surgery; Surgery, Radiation Therapy and BCNU vs. Surgery, Fractionated Radiotherapy and BCNU vs. Surgery, Radiation Sensitizer and Radiation Therapy followed by BCNU vs. Surgery, Radiation Therapy and Streptozotocin.

266. MICROWAVE IRRADIATION OF BRAIN THROUGH CRANIOPLASTY

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This is part of a broader project. A summary of this subproject is not available.

267. RADIOTHERAPY FOR CENTRAL NERVOUS SYSTEM TUMORS

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OBJECTIVE: To determine the indications for postoperative radiotherapy plus chemotherapy according to site and histology for central nervous system tumors.

APPROACH: Patients with histologically confirmed diagnosis of central nervous system tumors are eligible for study. The local failures are analyzed according to histology, tumor

volume, the quality of surgery and the irradiation technique. The postoperative irradiation will be supplemented with chemotherapy, i.e., BCNU.

268. MEASUREMENT OF NORMAL TISSUE CHANGE IN THERAPEUTICALLY IRRADIATED BRAIN (HUMAN)

Kramer, S., Thomas Jefferson University, Jefferson Medical College, Dept. of Radiation Therapy & Nuclear Medicine, *1025 Walnut St., Philadelphia, Pennsylvania*, 19107, United States of America

This is part of a broader project. A summary of this subproject is not available.

269. EFFECTS OF RADIATION THERAPY ON CELLULAR AND HUMORAL IMMUNITY OF PATIENTS WITH HEAD AND NECK CANCER (ABBREV)

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Accession of new patients has been closed, with 62 evaluable cases. The group randomized to adjuvant BCG/levamisole and the group receiving radiotherapy alone were reasonably comparable as to age, sex, site and stage. At entry, 64% showed impaired immunocompetence (as compared to age-matched controls without cancer). To date, there have been no significant differences between the immunotherapy and radiation only groups with respect to tumor control, disease-free interval, or survival curves. There were some variations between the two groups in the immunologic parameters, but these were not statistically significant. In vitro test results for all patients were as follows: T cell absolute numbers decreased at entry, with further fall at end of radiation, but recovery occurring at 8 weeks; T cell percentages decreased at entry, with no further changes after radiation or during follow-up to 40 weeks; B cell absolute numbers decreased at end of radiation, but with subsequent recovery maintained through 40 weeks; B cell percentages showed no significant alterations; blastogenesis (with PHA and PWM) decreased at entry, with further fall after radiation, and partial recovery during follow-up through 28 weeks; sialic acid levels elevated, with slight further rise at end of the radiation and gradual decrease toward normal at later follow-up. Lymphocyte cytotoxicity showed no apparent radiation effects, but has been discontinued because of complexity and variability of the results. Median survival had not been reached at last review. Monitoring of patients continues with periodic immunologic profiles. Further correlation of test results with clinical course and outcome with be made.

270. TREATMENT OF LOCALIZED ADVANCED HEAD AND NECK CANCER WITH HIGH DOSES OF INTERMITTENT RADIATION

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OBJECTIVE: To determine the effectiveness of high intermittent doses of radiation in the treatment of localized, advanced cancer of the head and neck.

MATERIAL: Patients with localized advanced head and neck cancer (T3, T4, and/or N3)

METHOD: Supervoltage radiation, 2,400 rads in 3 weeks (3 fractions). (Translated)

271. HYPOTHALMIC-PITUITARY FUNCTION AFTER HEAD AND NECK IRRADIATION (CHILDREN)

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This is part of a broader project. A summary of this subproject is not available.

272. PARATHYROID DISEASES ASSOCIATED WITH IRRADIATION

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There have been scattered reports showing that parathyroid adenoma and hyperplasia with hyperparathyroidism were associated with irradiation to the head and neck areas for benign diseases in childhood. To delineate this relation 30 documented cases with parathyroid adenoma or hyperplasia are being surveyed by mail questionnaire. The prevalence of hypercalcemia and hyperparathyroidism in more than 1,000 cases from the thyroid screening program where all that patients had radiation therapy for benign diseases in childhood or young adulthood, and in 300 patients with malignant lymphoma who have been treated with radiation therapy to the neck area, is also being examined.

273. RADIOIODINE TREATMENT OF THYROID CANCER

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This study continues follow-up of patients treated for thyroid cancer by radioiodine from 1946 to date, to determine incidence of other, possibly radiation-induced, malignancies; in addition, the radiation-absorbed dose in organs, in which any excess of such malignancies occurs, will be estimated. Since this therapy involves quantitative measurements at the time of treatments, and prolonged follow-up test doses, good tissue dosimetry is available and follow-up efficiency is high (96% in 1969). Data to 1967 were for 1,050 patient-years at risk, half of this total corresponding to those with 10 or more years of follow-up.

274. RADIATION-ASSOCIATED THYROID CARCINOMA

DeGroot, L. J., Refetoff, S., University of Chicago, Pritzker School of Medicine, Dept. of Medicine, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

An attempt is being made to find patients who had radiation to the thyroid area in childhood, study them intensively by clinical and laboratory means, and detect the presence or absence of thyroid carcinoma. Patients who have possible tumors as a result of radiation are treated by thyroidectomy. The natural history of the thyroid tumors and the value of surgery, prophylactic thyroid hormone suppression, and radioactive iodide therapy of the neoplasms, as well as immunological methods for control of metastatic disease, are being studied.

275. EFFECT OF RADIATION ON SALIVARY GLANDS

Cogan, M. I., Kamath, C. R., Gill, S. P., Kunyosying, U., Smith, N. J., Blundell, G. P., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Dental Service, *Martinsburg, West Virginia*, 25401, United States of America

The original purpose of this project was to correlate the values obtained from diagnostic tests used to determine changes in salivary composition and salivary gland function and structure in patients undergoing radiotherapy for head and neck malignancy.

Because of the limited number of patients who received radiotherapy to the head and neck, it was decided to examine only the diagnostic value of sialographic and scintigraphic tests conducted to determine changes in salivary gland disorders.

In this study the patients with chronic sialadenitis had normal sialograms; however, one patient showed no radioactivity uptake while another patient showed reduced radioactivity concentration in the affected salivary glands.

The typical sialographic picture of a patient with a mixed tumor was displacement of the ducts around the mass. The observation of reduced radioactivity on a smooth margined radionegative (cold) lesion on scintography merely confirmed the findings of the sialogram.

A smoothly margined radiopositive (hot) lesion was considered to be strongly suggestive of a Warthin's tumor on the basis of the case in this study. In a patient undergoing radiation therapy, the chronic and apparently permanent damage sustained by the gland at intervals was manifest by the incomplete filling of the gland on the sialograms; these findings were consistent with the reduced radioactivity seen on the salivary gland scans.

It was concluded from this project that contrast sialography and radionuclide scanning were complementary procedures used in the evaluation of the salivary glands.

276. A RANDOMIZED STUDY FOR THE TREATMENT OF CHROMOPHOBE ADENOMAS OF THE PITUITARY GLAND WITH IRRADIATION

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Since the natural history of chromophobe adenomas unassociated with visual impairment is uncertain, the approach to therapy in patients with this disorder is controversial. Complications often attributed to tumor growth may, in fact, be sequalae of the treatment administered, whether it be radiotherapy or surgery. The purpose of this project is twofold: 1) To observe the natural history of untreated chromophobe adenomas in patients who do not present initially with visual disturbances and 2) to compare their clinical course with that of patients treated by one commonly employed modality, i.e., radiation therapy. Thus, patients will be randomized into two groups: one group will receive no therapy and one group will be treated with conventional pituitary irradiation. In a sense each group is serving as a control for the other group. Over the study period specific clinical and laboratory abnormalities will be assessed in each group and compared in an attempt to help guide physicians in the treatment of this disorder.

277. EVALUATION OF PITUITARY ADENOMA IRRADIATION (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

278. PREFERENTIAL KILLING OF MELANIZED TISSUES

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An intensive effort has been made toward the development of non-ionizing radiation in the treatment of human neoplasms. These investigations have been guided by two biological principles: 1) the melanins have been found to be biologically amorphous semiconductors and have anomalously high ultrasound absorption coefficients, and 2) elevated temperatures in the 40-50 degrees C temperature range may have significant anti-tumor activity.

In vitro studies using elevated temperatures between 41 degrees and 44 degrees C have demonstrated synergism between these temperatures and the chemotherapeutic drugs cis-platinum and mitomycin-C. The primary mechanism for the potentiation of these drugs was found to be inhibition of enzymatic removal of DNA cross-links created by these drugs.

Plane wave ultrasound and localized alternating magnetic field systems have been developed and Phase I/II studies have been carried out in humans. The first 50 patients studied have shown an overall objective response rate of 55% for tumor temperatures between 42 degrees and 46 degrees C with no correlation between ultrasound and magnetic field dose and anti-cancer activity. All tumors treated above 47 degrees C responded. Fifteen patients were also treated with a combination of ultrasound and ionizing radiation; nine of these patients were diagnosed as having malignant melanoma. The objective response rate with this form of therapy was 100% with a complete response rate of 60%.

279. LATE EFFECTS IN CHILDREN AND ADULTS OF 224RA INJECTIONS

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Nine hundred patients treated with 224Ra for tuberculosis, ankylosing spondylitis and other diseases, mainly during the years 1946-1951, have been followed up over a 30-year period. Fifty cases of bone sarcomas and 4 cases of chondrosarcomas have been found, of whom 36 cases had been treated with 224Ra as juveniles and 18 as adults. Follow-up continues.

280. SARCOMA RESPONSE TO X-RAYS (HUMANS, HAMSTERS)

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This is part of a broader project. A summary of this subproject is not available.

281. SELECTIVE IRRADIATION OF OSSEOUS TUMORS WITH 33P-HEDP

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No summary has been provided to the Smithsonian Science Information Exchange.

IV. RADIATION INJURY AND PATHOLOGY

282. PROTECTION FROM RADIATION INJURY OF NORMAL TISSUES

Travis, E. L., Fowler, J. F., DeLuca, A. M., Sanders, C. J., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Radiobiology Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

A series of sulfhydryl compounds has been developed by Walter Reed Army Institute, which protect normal tissues against radiation injury. WR 2721, one drug in this series, gives a dose modifying factor (i.e., ratio of radiation doses that give the same level of biological damage with the drug as without the drug) ranging from 1.2 to 2.5 depending on the normal tissue tested. This drug has been shown not to protect murine tumors from radiation. This drug is now being used in clinical trials in radiation therapy. The purpose of this work is to study the ability of this drug to protect a rapidly proliferating and slowly proliferating tissue, i.e., skin and lung respectively, in mice, and to compare this drug with other radioprotectors available from Walter Reed.

283. METHOD FOR PROTECTION FROM RADIATION INJURY

Coller, J. A., Salzman, F. A., Curby, W. A., Lo, T. C., Lahey Clinic Foundation Inc., Dept. of General Surgery, *605 Commonwealth Ave., Boston, Massachusetts*, 02215, United States of America

The primary objective of this program is to minimize or eliminate radiation injury to the small bowel during high dose pelvic irradiation. The effort is specifically directed towards application to preoperative high dose adjuvant irradiation in the treatment of high-stage, non-metastatic bladder cancer. The approach is a method that mechanically displaces the small bowel from the field of irradiation, during the period of radiation delivery.

The proposed method involves the insertion of an inflatable, biologically inert (Silastic) space-occupying device into the pelvis and lower abdominal cavity. During the same procedure, urinary diversion would be accomplished with an ileal-loop (high). During a subsequent course of 6000 Mev irradiation, the Silastic device would prevent small bowel, cecum, and sigmoid colon from entry into the irradiation field. Following the course of radiotherapy a second operative procedure would be undertaken at which time the device would be removed and cystectomy performed.

284. CHARACTERIZATION OF RADIATION-RELATED CARDIAC INJURY

Byhardt, R. W., Llaurado, J. G., Gillin, M., Kline, R., Bamrah, V. S., Gross, C. M., Kun, L., Cox, J. D., Gunn, W., Swartz, H., Wann, L. S., Soin, J., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *5000 W. National Ave., Wood, Wisconsin*, 53193, United States of America

The purpose of this study is to determine the incidence and nature of radiation-related cardiac injury (RRCI) as related to the pericardium and/or myocardium in patients receiving incidental cardiac irradiation during treatment for non-small cell carcinoma of the broncho-pulmonary tree. In addition to char-

acterizing the acute, sub-acute and chronic effects, the study will attempt to correlate the incidence and severity of RRCI to radiation dose and volume of heart irradiated. We will investigate the role of 99m technetium pyrophosphate cardiac scanning, nucleotide ventriculography, and m-mode and cross-sectional echocardiography in detecting and evaluating RRCI. All patients seen and accepted for curative radiation therapy with Stage I-III non-small-cell carcinoma of the lung whose volume of irradiated heart exceeds 50% of the total cardiac volume will be investigated by a battery of laboratory, x-ray, radionuclide and ultrasound tests. These tests will be repeated periodically during and after irradiation for at least three years or as long as the patient survives his disease.

285. STUDY OF CARDIOVASCULAR RADIATION INJURY

Fajardo, L. F., Brown, J. M., Hahn, G., McDougall, I. R., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Laboratory Service, *3801 Junipero Serra Blvd., Palo Alto, California*, 94304, United States of America

Two projects have been carried out: I. Pathogenesis of radiation nephropathy: Sequential study of irradiated murine kidneys has continued by electron microscopy: kidneys subjected to single dose radiation of 300 to 2500 rad, and kidneys subjected to fractionated irradiation of 1750 to 5950 rad. Since this portion of the project has not been completed no conclusions have been drawn so far.

II. Pathogenesis of veno-occlusive liver disease (VOD) after radiation: Liver samples from 11 patients with VOD were investigated by light (muliple staining techniques) and electron microscopy. Although usually undetectable by light microscopy, all samples contained fibrin in the central vein indicating that fibrin deposits precede the fibrillar (collagen) obstruction of these vessels.

BIBLIOGRAPHIC REFERENCES: Fajardo, L.F., Colby, T.: Pathogenesis of veno-occlusive liver disease after radiation. Arch. Pathol. Lab. Med. 104:548-588, Nov., 1980. Eltringham J.R., Fajardo, L.F., Steward J.R., Kauber M.L. Investigation of Cardiotoxicity in Rabbits from Adriamycin and Fractionated Cardiac Irradiation: Preliminary Results. Frontiers of Radiation Therapy and Oncology 13:21-25, 1979.

286. RADIORESISTANCE OF LYMPHOCYTES IN A CASE OF PROLYMPHOCYTIC LEUKEMIA

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Prolymphocytic leukemia is a rare variant of chronic lymphocytic leukemia (CLL) distinguished from the classical disorder by the morphology of the lymphoid cells and by characteristic clinical symptomatology (Galton et al., British Journal of Haematology, 1974, 27, 7). In the present case, the lymphocytes were found to show several additional peculiar features (Publication No. 207). The majority had markers of both 'T' and 'B' lymphocytes, but in common with CLL=lymphocytes the majority were colchicine ultrasensitive. Unlike CLL-lymphocytes or normal lymphocytes they were highly radioresistant in vitro.

Exposure of the patients' peripheral blood lymphocytes to the highest dose of radiation tested (500 R) elicited only 15 percent death during a subsequent two-day period. Mortalities recorded previously for normal and CLL lymphocytes were higher and particularly so in CLL where they measured 40-87 percent.

Although the patient radiation response - as expressed by a plot of the logarithm of lymphocyte survival against radiation dose (0-500 R) -could be drawn as a straight line, it was considered impermissible to extrapolate it to doses above 500 R even if the remaining 85 percent of the population were assumed to be equally radiosensitive. Theoretical considerations have shown that the radiation response of a homogeneously radiosensitive population that remains incompletely lethally irradiated up to the highest dose tested will be non-linear at any time of analysis prior to death of all the lethally irradiated cells. Moreover, according to a mathematical equation that predicts the shape of the radiation response where death rate is governed by first order kinetics (ICRF Scientific Report 1976 - report 113) the response at the most lethally ineffective doses will appear linear. Extrapolation of the experimental findings in accordance with this equation gave 2,500 R as the estimate of radiosensitivity (i.e. the dose permitting 37 percent survival). This value denotes marked radioresistance when compared with values all less than 400 R found for CLL-lymphocytes, normal T lymphocytes or normal B lymphocytes.

287. RADIOPROTECTIVE AND THERAPEUTIC ACTION OF LEUCOTROFINA AND THYMUS FRACTION B

Uray, Z. A., Ban, C. I., Maniu, M., Institutul Oncologic Cluj-Napoca, Laboratory of Nuclear Medicine, *34-36 Republicii, 3400 Cluj-Napoca, Romania*

OBJECTIVES: Prevention of leuco-, lympho-, and erythropenia with thymic extracts in patients subjected to intense radiation therapy. Treatment of radiation sickness. Experimental extracts - Leucotrofina (calf thymus extract), isolated by Lab. Ellem, Milano - Italy; thymus fraction B (calf thymus extract) isolated by Inst. of Endocrinology, Bucharest - Romania.

APPROACH: (1) Therapeutic effect of Leucotrofina upon the survival of mice exposed to gamma radiation in the range of sublethal and lethal doses (500-900 rad); (2) dynamic studies of radioiron (59-Fe) incorporation into erythrocytes in mice irradiated with 100 rad and pre-treated or post-treated with thymus fraction B and Leucotrofina; (3) changes in 59-Fe splenic and bone marrow uptake and spleen weight on the 9th day after irradation and Leucotrofina application; (4) the effect of Leucotrofina upon endogenous spleen colonies (ESC) formation in irradiated mice (500 R); (5) complex hemathological biochemical and isotopic investigations (1979).

PROGRESS: (1) The LD 50/30 for the intreated group was estimated at 570 rad while after Leucotrofina treatment (6x0.2 ml daily after irradiation) the value rose to 690 rad. The dose reduction factor (DRF) was 1:21. (2) The radioiron uptake 3 days after irradiation (100 rad) for the untreated group was estimated at 37.7%, for the untreated irradiated group 10.5% and for the treated group with thymus fraction B at 23.2%, with Leucotrofina at 23.7%. (3) Total irradiation with 500 rad leads to a significant decrease in 59-Fe splenic and bone marrow uptake estimated on day 9 post-irradiation (respectively 5.35% and 0.64%). Administration of Leucotrofina (6x0.2 m. daily) reduces significantly the decrease in spleen weight and in iron uptake respectively in spleen and in bone marrow (respectively 10.3% and 1.01%). (4) The number of ESC 9 days after irradiation (300 rad) was estimated at 8.5 in controls. Application of Leucotrofina (6x0.2 ml after irradiation) results in an increase in ESC counts: 15.3.

288. AUTOLOGOUS BONE MARROW GRAFTING IN PATIENTS SUBMITTED TO RADIATION THERAPY - TOTAL BODY IRRADIATION AND PATHOLOGIC STUDIES (ABBREV)

Falcetti, E., Loasses, A., Mandelli, F., Meloni, G., Universita degli Studi di Roma, Istituto Radiologia, *c/o Policlinico Umberto I, Rome, Italy*

Cryopreserved autologous bone marrow infusions were performed by F. Mandelli and co-workers on 6 paticnts affected by acute or chronic myeloid leukemia at the Hematology Department, University of Rome. Results are not reported here.

TBI with 4 MeV or 6 MeV Linac X-rays was carried out on 38 patients. (1) Fifteen patients affected by stage III or IV non-Hodgkin's lymphoma. Dosage schedule: 10 rads per fraction; 2 fr. per week; mid-plane total dose 50-240 rads. (2) Fourteen cases of ALL, after the second relapse following chemotherapy. Dosage schedule: 10 to 30 rads per fraction; 2 fr. per week; total mid-plane dose 150-225 rads. (3) Nine patients affected by ANLL, after first C.R. following chemotherapy. Dosage schedule of short-term TBI: 12.5 rads per fraction; 2 fr. per day separated by a 12-hour interval, for 5 consecutive days; total mid-plane dose 125 rads. Clinical results are under evaluation. Preliminary data on the tolerance: nadir values of platelets reached at 4-7 weeks in the majority of cases. Thrombocytopenia varied from 80,000 to 10,000 cells/microliter. Critical values appear to be unrelated to initial pre-irradiation counts, and are mainly dependent on single fraction dose. Granulocyte and lymphocyte counts oscillate widely; the reliability of cyclical models of various types of blood cell concentration is under consideration. ST-TBI was well tolerated. This last method appears to be a useful tool for studies on the association of radiation therapy and chemotherapy.

In a group of 18 patients affected by non-Hodgkin's lymphoma, cells of bone marrow and of peripheral blood were cultured as described by Pike and Robinson (1970). The appearance of colonies and clusters was recorded. Sixteen out of eighteen cases gave positive cultures. No definite results appeared related to clinical data. Effects of substitution of different types of feeder layers on colony formation from cell suspension of bone marrow were successively examined. Studies on cultures of lymphoma stem cells are in progress.

289. CHROMOSOME ABERRATIONS INDUCED BY DIFFERENT KINDS OF RADIATION AND THEIR USEFULNESS AS BIOLOGICAL INDICATORS OF THE RADIATION DAMAGE

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The problems of radiation cytogenetics are extremely topical as it is clear that detailed studies on the effects of radiation on the human chromosomes are indispensible for the quantitative evaluation of the harmful effects on the hereditary structures and consequently, for the elaboration of scientifically well-founded measures which ensure radiation safety.

According to the program for the time period covered, the qualitative and quantitative analysis of chromosome aberrations induced in human lymphocytes by fission neutrons will be performed. Human peripheral lymphocytes will serve as the biological mode. Lymphocytes will be irradiated in blood immediately after bleeding. Irradiation by fission neutrons will be carried out at the experimental nuclear reactor IRT-2000 at Sofia with various neutron flux densities. The object of the chromosome analyses will be identification of the following chromosome anomalies: chromatide fragments, chromosome fragments, dicentrics and polycentrics, minutes, rings, total of aberrations and total of aberrant cells. A mathematical model will be developed for the dose-response relationships for the different chromosome anomalies.

290. RISK OF SOMATIC RADIATION DAMAGE - EPIDEMIOLOGICAL INVESTIGATIONS ON RADIATION DAMAGE IN PATIENTS TREATED WITH RA-224

Goessner, W., Spiess, H., Wick, R. R., Gesellschaft fuer Strahlen und Umweltforschung mbH Munchen, Abteilung fuer Pathologie, *Ingolstaedter Landstrasse 1, D8042 Neuherberg, Federal Republic of Germany*

In about 2,000 persons treated with radium-224 for ankylosing spondylitis (Bechterew's Disease) or bone tuberculosis, the effects of this particular type of radiation are being investigated. In collaboration with orthopedic hospitals the patients are subjected to a follow-up examination. The results of these investigations, in particular the onset of malignant and degenerative disease and causes of death, are evaluated with a view to establishing dose-response. Further knowledge about the risk of radiation cancers in general is thus gained.

291. FOLLOW-UP STUDY OF PATIENTS TREATED BY X-RAY EPILATION FOR TINEA CAPITIS

Albert, R. E., Shore, R. E., Pasternack, B. S., New York University, School of Medicine, Dept. of Environmental Medicine, *100 Washington Sq. E., New York, New York*, 10003, United States of America

Children treated for tinea capitis between 1940 and 1959 at a major New York City dermatology clinic have been followed to examine the tumourigenic effects of X-radiation to the head (300 - 400 R). Some 2,215 irradiated patients and 1,395 patients given medications for tinea capitis have been traced. The groups are very well matched on sex, race, age and socioeconomic status. A third survey of these groups (average interval since tinea treatment - 20 years) is in progress and is showing a continued excess of basal cell carcinomas, and brain, thyroid and parotid tumors in the irradiated group.

292. COMPLICATIONS RESULTING FROM IRRADIATION TO THE PELVIS

Mantyla, M., Minkkinen, J., Middle Finland Central Hospital, Dept. of Radiotherapy, *Sadesairaala, 40620 Jyvaskyla 62, Finland*

The purpose of the present study is to clarify complications following pelvic irradiation.

The material consists of 500 patients. All patients have undergone pelvic irradiation in the Middle Finland Central Hospital Radiotherapy department and have been undergoing follow-up examinations regularly at three-to-six-month intervals.

293. BOWEL CHANGES FOLLOWING THERAPEUTIC RADIATION FOR PELVIC CANCER (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

294. THE EFFECTIVENESS OF A NEW CHEMICAL APPROACH IN PREVENTING POST-IRRADIATION CARIES

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Patients receiving radiation therapy for malignancies of the head and neck are placed on a preventive program where 0.4% stannous fluoride, either alone or in combination with acidulated phosphate fluoride, is used to control the ravaging form of post-irradiation dental caries which primarily is a result of the remarkable decrease in salivary flow and the resulting xerostomia. Edentulous patients and those with full-mouth extractions are followed for bone healing and incidence of osteoradionecrosis. A total of 423 patients are included in the study with follow-up ranging from 3 months to 7 years.

Collection of whole saliva and parotid fluid with measurement of flow rates has shown the remarkable reduction in salivary flow in relation to increasing total radiation. Minimal flow rate resulted after as little as 450 rads and after minimal flow was reached no recovery of salivary generation was evident. When radiation field arrangement, amount of salivary gland included, dose, and initial flow rate are compared to resulting flow rate the upper border of the field is a critical factor when using parallel opposed fields to be the lateral face. Most of the parotoids have to be outside the fields to prevent severe dryness. Neck fields which do not encompass salivary gland do not decrease secretion. Over 600 saliva samples have been collected to monitor flow rates and IgA levels. Additional patients will be accessioned for further evaluation of IgA levels in whole saliva and parotid fluid from the same patients. Measurement of IgA is made by rocket immunoelectrophoresis.

295. RADIATION PRODUCED HUMAN PULMONARY LESIONS

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This is part of a broader project. A summary of this subproject is not available.

296. STUDY OF EVENTUAL ALTERATIONS OF THYROID FUNCTION IN THE IRRADIATION OF HEAD AND NECK TUMORS

Soares, W. E., Serson, D., Nunes, J. E., Schmillevitch, J., Peres, O., Hospital A.C. Camargo, Departamento de Radioterapia, *Rua Prof. Antonio Prudente 211, Sao Paulo 01509, Sao Paulo, Brazil*

OBJECTIVE: To study thyroid function in patients with head and neck tumors in whom the thyroid was included in the irradiation field. High energy equipment (4 MeV Linear Accelerator) was used with a dose of 5,000 rads in 5 weeks with an average T.D.F. of 82.

METHOD: The assessment of thyroid function is performed through uptake, scanning, T3 retention and T4 saturation tests before and after radiotherapy, as well as 3 months after the end of treatment.

297. FOLLOW-UP STUDY OF PERSONS WHO HAD I 131 AND OTHER DIAGNOSTIC PROCEDURES DURING CHILDHOOD

Hamilton, P. M., U.S. Dept. of Health & Human Services, Public Health Service, Food & Drug Admin., Bureau of Radio-

logical Health, *5600 Fishers Ln., Rockville, Maryland,* 20857, United States of America

The objective is to assess the risk of development of thyroid neoplasms following exposure to I 131 by evaluating the thyroid neoplasm experience in young adults who received diagnostic I 131 during childhood, compared to the experience in a similar group of unexposed young adults and a group of unexposed siblings.

298. THYROID DYSFUNCTION AFTER RADIATION EXPOSURE TO HEAD AND NECK (HUMAN)

Nicoloff, J. T., University of Southern California, School of Medicine, Dept. of Medicine, *2025 Zonal Ave., Los Angeles, California,* 90033, United States of America

This is part of a broader project. A summary of this subproject is not available.

299. PSYCHOSOCIAL CONSEQUENCES OF RADIOTHERAPY

Heuvel, W. J., Studicentrum voor Soc. Oncologie, *Plesmanlaan 121, Amsterdam, Netherlands*

OBJECTIVE: Inventory of side effects, personal discomfort, psychological and social problems following and due to radiotherapy in cancer patients. Firstly, what are the disadvantages of this type of treatment according to the patient despite the benefits, and how does the patient react to these disadvantages; what are his opinions about the treatment? And secondly, how can the desire for improvement resulting from this investigation be met; what are the alternatives for better care and guidance in connection with this type of treatment? How can the procedure of radiotherapeutic treatment be improved for the patient? What is and should be the task of the radiotherapist, the laboratory worker and the nurse?

APPROACH: Patients of the outpatient clinics of several cancer hospitals will be interviewed at various stages of the radiation treatment and after the treatment has been completed. In this series of interviews the patient will be encouraged to discuss his personal views, and the reactions he experienced. Various alternative setups of psychosocial care, absence of such care, etc., will be compared. Satisfaction of patients in these setups will be evaluated.

300. COMPLICATIONS OF RADIOTHERAPY

Van Den Heuvel, W. J., Inst. of Social Oncology, *Dr. Molewaterplein 50, Postbus 1738, 3000 DR Rotterdam, Netherlands*

This project will consist of a longitudinal study of patients' experiences with radiotherapy, the physical and emotional complications of this kind of treatment and the impact these complications have on the patients' private and social lives.

The object of the study is to obtain more systematic knowledge of these factors and their interrelations, as well as to discover personality characteristics common to patients who develop such complications. Thorough knowledge of personality characteristics associated with complications is a prerequisite of effective prevention, which is of course the ultimate goal of all research work of this kind. Questions to be dealt with are: 1. In what ways do patients experience radiotherapy (dependence on staff of the clinic or unit, anxiety, expected outcome, support and care)? 2. Which physical and emotional complications occur? 3. What is the impact of treatment and what changes does it bring about in the patient's social life (job, family, friends)? 4. What correlations can be found between findings pertaining to issues mentioned in questions 1-3, and individual and social characteristics of the patients in the study (type of cancer, type of treatment, prognosis, age, education, life style, personality, social life)? 5. What correlations can be found between findings pertaining to issues mentioned in questions 1-3, and different ways of providing support and care to the patient (information, support, understanding, support in immediate social environment).

SAMPLE: The sample should be stratified by a number of variables (type of cancer, amount of radiation given, patients who have and who have not had surgery, and patients who have received palliative treatment and patients who have not received such treatment) in order to measure the effect of radiotherapy on the different conditions patients receiving the treatment may be in. For practical purposes the sample should be limited to out-patients of 6 radiotherapy clinics or units varying in approach toward patient and treatment (role of social work, difference between university and regional clinics). From each clinic, 160 patients will be included in the study, amounting to a total of 960 participants.

DATA COLLECTION: All patients will be asked to participate in three interviews and to complete several questionnaires, as part of the interview.

301. EFFECT OF MAGNETIC FIELD AND RADIATION ON TUMORS IN VITRO AND IN VIVO

Chandra, S., Stefani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Therapeutic Radiology Service, *5th Ave. & Roosevelt Rd., Hines, Illinois,* 60141, United States of America

The effect of low doses, 50, 100 and 300R, of X-rays on the ultrastructure of a human bronchogenic carcinoma and a Burkitt's lymphoma was studied. Following irradiation the cells were incubated at 37 degrees for different periods of time and examined by electron microscopy. The plasma membrane of the lymphocytes and the bronchogenic carcinoma cells exhibited localized protrusion. The Burkitt's lymphoma cells showed only breaks or fenestration of the surface membrane. The study suggests that the plasma membrane of mammalian cells may be one of the primary sensitive targets where the radiation induced injury occurs first. We hypothesize that the radiation-induced protrusion of the plasma membrane is caused by certain topographical changes in the membrane which result in an alteration of the membrane elasticity or tensile strength at the site of radiation injury. Hyperthermia is being suggested as a possible adjunct to radiation therapy in the treatment of human tumors. We are presently studying the effect of hyperthermia, 1 hour at 43 degrees or 45 degrees C, on the ultrastructure of cells in vitro.

302. HYPOSPERMIA AND ASPERMIA AFTER RADIATION THERAPY (HUMAN)

Rubin, P., University of Rochester, School of Medicine & Dentistry, Dept. of Medicine/Radiology/Surgery, *601 Elmwood Ave., Rochester, New York,* 14627, United States of America

This is part of a broader project. A summary of this subproject is not available.

303. QUALITY OF LIFE, MORBIDITY IN SURVIVORS AFTER DEFINITIVE RADIATION THERAPY

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This is part of a broader project. A summary of this subproject is not available.

304. CLINICAL INVESTIGATIVE RADIATION PATHOLOGY

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This is part of a broader project. A summary of this subproject is not available.

305. RADIATION PATHOLOGY - TUMOR MICROVASCULATURE RESPONSE (HAMSTERS, HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

V. RADIATION DOSIMETRY AND DOSE FRACTIONATION STUDIES

306. ENHANCED ORAL CARCINOGENESIS BY LOW DOSE X-RADIATION

Lurie, A. G., University of Connecticut, Health Center, School of Dental Medicine, Dept. of Oral Diagnosis, *Farmington Ave., Farmington, Connecticut,* 06032, United States of America

The tissues of the human oral cavity are frequently exposed to repeated low doses of known and suspected carcino-

gens such as tobacco and x-radiation from diagnostic medical and dental sources. Prior studies in our laboratory have shown synergy between concurrent applications of DMBA and exposures to modest levels of x-radiation in hamster cheek pouch tumorigenesis. This synergy was manifested by greater tumor incidence, shorter latent period, and greater tumor volume in animals receiving combined treatments than in animals receiving either treatment alone. We have also shown that low-level x-radiation causes a significant late increase in pouch vascular volume and that there is a significant interaction between the effects of x-radiation and DMBA-induced tumors on pouch functional vasculature. Ongoing studies are examining the effects of decreasing radiation doses on DMBA-induced tumor incidence and progression as well as the possible mechanistic role of radiation-induced hemodynamic changes in the induction and progression of these tumors. Young adult male Syrian golden hamsters have received various doses of DMBA to the cheek pouch accompanied by repeated exposures of 1-20R x-radiation at weekly intervals. The temporal relationships between applications of the chemical and radiation have varied. Animals are being observed for varying lengths of time; tumor latency, volume, incidence, histopathology and hemodynamics are being studied using observational, histopathological and radioisotopic techniques. It is anticipated that the results of these studies will clarify dose-response relationships and time-dose relationships of low level x-radiation in this system, leading to a more quantitative basis for calculations of human radiation risk estimates. Additionally, the data should provide information on the nature of radiation induced hemodynamic changes in the induction of epithelial neoplasms by low level exposures to multiple environmental carcinogens.

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307. EVALUATION OF RADIOTHERAPY DOSE VARIABILITY DUE TO LUNG DENSITY PERTURBATIONS IN CANCER OF THE LUNG

Fullerton, G. D., Mira, J. G., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Radiology Service, *San Antonio, Texas,* 78284, United States of America

The purpose of this project is to determine the extent of lung density and density distribution variations in patients undergoing radiation therapy to determine if these parameters cause significant error in radiation dose delivery. Patients are offered CT scans to measure the above parameters; these data are then used to calculate the extent of dose distribution variations. Data have been accumulated on over thiry (30) patients and preliminary evaluations have shown significant increases and, more surprisingly, decreases in lung density with tumor growth. The further evaluation of dose variations has been postponed until April when a more accurate calculation algorithm will be available with the purchase of a TP-11 treatment planning system at the Cancer Therapy and Research Center.

Preliminary results appear to indicate that lung density evaluation with CT will provide a significant improvement in dosimetry. Project will be completed this fall.

308. MEAN MARROW DOSE AND 'LEUKEMIA DOSE' OF THE SWISS POPULATION (1978)

Poretti, G. G., Ionesco, F., Garavaglia, G., Universitat Bern, Radiuminstitut, Dept. of Medical Radiation Physics, *c/o Inselspital, CH3010 Bern, Switzerland*

OBJECTIVE: Calculation of the mean marrow dose and of the 'leukemia dose' of the Swiss population (1978-79).

APPROACH: The 'annual mean marrow dose of a population' can be calculated from the single doses received from each part of active bone marrow irradiated in the course of an X-ray examination and, as in the case of the genetically significant dose, from the demographic data. The annual mean marrow dose (1971) for the Swiss population was tentatively calculated using the values of the mean marrow dose per examination of the UK survey of 1957/58 and amounts to about 121 mrad. Barium meal contributes about 30% of the total; intravenous pyelography, barium enema, lumbar spine and mass miniature radiographies each account for about 10%.

PROGRESS: Experimental measures and calculation of the mean marrow dose of the Swiss population. Low dose radiation burden of a population in connection with the increase of the (myelotic) leukemia cases.

309. DOSE RESPONSE RELATIONS FOR LOCALIZED BONE MARROW IRRADIATION (RABBITS, HUMAN)

Rubin, P., University of Rochester, School of Medicine & Dentistry, Dept. of Medicine/Radiology/Surgery, *601 Elmwood Ave., Rochester, New York,* 14627, United States of America

This is part of a broader project. A summary of this subproject is not available.

310. RADIATION DOSE RATE EFFECTS ON THE HEMATOPOIETIC SYSTEM (MAN)

Fischer, J. J., Yale University, School of Medicine, Dept. of Therapeutic Radiology, *333 Cedar St., New Haven, Connecticut,* 06510, United States of America

This is part of a broader project. A summary of this subproject is not available.

311. DOSIMETRIC KINETIC STUDY OF OSTEOTROPHIC COMPOUNDS

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OBJECTIVE: To determine the characteristics of osseous accumulation, blood clearance and renal excretion, as well as dosages received in different organs from osteotrophic compounds used in the detection of bony metastasis by gammagram.

METHOD: Experiments are performed involving the kinetics of radiotracers in experimental animals and in humans. In humans, determinations of in vivo activity are performed on different organs (liver, spleen, kidneys, heart, soft tissue, etc.) and urine and blood samples are taken. In experimental animals data are obtained on the activity of the compound on a gram of tissue at various times after administration. Gammagrams and radiologic analyses are performed on all study patients.

PROGRESS: Thirty patients have been studied in accordance with the above-mentioned scheme using In-STPP, a radiopharmaceutical synthesized in the Radiopharmacy Laboratory at our Institute. In addition, these studies have been carried out in a large number of experimental animals.

We are presently working on a dosimetric study based on accumulated information, and also on an explanation of the compound's behavior using compartmental simulation. We expect to extend this procedure to the study of other new compounds shortly.

312. MAGNETIC ENHANCEMENT OF ELECTRON DOSE DISTRIBUTIONS

Nath, R., Schulz, R. J., Weinhous, M. S., Yale University, School of Medicine, Dept. of Therapeutic Radiology, *333 Cedar St., New Haven, Connecticut,* 06510, United States of America

The role of intense magnetic fields in the enhancement of dose distributions of high energy electrons is being investigated. This project is based on the premise that an increase in the ratio of tumor dose to normal tissue dose will increase cure rates and decrease morbidity in cancer patients who receive radiation therapy. We are simulating the transport of high energy electrons in the presence of magnetic fields using the Monte Carlo technique. It has been shown that a transverse magnetic field of 20-50 kilogauss enhances percent dose at a depth of 10 cm compared to the entrance dose by a factor of 1.5 to 2.0, and a longitudinal magnetic field significantly reduces the penumbra of the electron beams. Effects of different magnetic field profiles are being investigated in order to determine quantitatively the improvement in dose distributions by practical magnet systems. The effects of magnetic fields from magnets designed for clinical use on the dose distributions produced in an anthropomorphic phantom will be determined and an optimum design for a clinical magnet will be achieved.

313. ELECTRON THERAPY DOSIMETRY BASED ON THE FERMI AGE THEORY

Lanzl, L. H., Jette, D., University of Chicago, Pritzker School of Medicine, Dept. of Radiology, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

This research has as its objective the development of a practical and precise method for determining absorbed-dose distributions from high-energy electron beams for use in cancer treatment planning, particularly in cases complicated by inhomogeneities such as bone and lung tissue, and by body curvature. This will be accomplished by generalizing the Fermi age diffusion theory, already successfully employed in nuclear reactor physics, to the dosimetry of high-energy electron beams. In order to test and further refine the Fermi age model, experiments simulating various inhomogeneities are being carried out. Our final goal is to develop an algorithm for computer calculation of dose distribution from high-energy electron beams, applicable to realistic clinical situations.

314. MODIFICATION OF ELECTRON BEAM DOSE DISTRIBUTIONS BY MAGNETIC FIELDS

Paliwal, B. R., University of Wisconsin, Madison Campus, Medical School, Dept. of Human Oncology, *450 N. Randall Ave., Madison, Wisconsin*, 53706, United States of America

This is part of a broader project. A summary of this subproject is not available.

315. HIGH ENERGY X-RAY AND ELECTRON BEAM DOSIMETRY

Schulz, R. J., Yale University, School of Medicine, Dept. of Therapeutic Radiology, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

This is part of a broader project. A summary of this subproject is not available.

316. BASIC PHYSICAL DATA FOR NEUTRON DOSIMETRY

Finlay, R. W., Ohio University, Athens Campus, School of Arts & Sciences, Dept. of Physics, *Athens, Ohio*, 45701, United States of America

Clinical application of neutron radiotherapy has expanded rapidly in recent years, but progress in precision neutron dosimetry has been hampered by a lack of basic nuclear physics data. The problem is most severe for those clinical facilities which produce neutron spectra having a substantial fraction of neutrons with energy greater than 20 MeV. In this energy region there is no adequate data base for the calculation of significant dosimetry quantities such as the relative response of 'tissue-equivalent' dosimeters. These calculations are required if the delivered dose to tissues of various chemical composition is to be related with confidence to the dosimeter response. Until recently, few laboratories were equipped to perform the required measurements.

Ohio University, in conjunction with Lawrence Livermore Laboratory, is developing a new magnetic-quadrupole-triplet spectrometer. This spectrometer will be used with the Ohio University intense neutron source to provide an efficient, flexible technique for the measurement of neutron-induced reactions. Specifically, we propose to measure the angle- and energy-dependent cross sections for the production of protons, deuterons and alpha particles by 20-26 MeV neutrons incident on carbon, nitrogen and oxygen. Moreover, an effort will be made to measure directly the entire energy spectrum (1.0 less than Ep, alpha less than 26 MeV) of charged particles produced by high energy neutrons incident on tissue-equivalent plastics, e.g., Shonka plastic A-150. Such a measurement would provide both an internal consistency check on the individual measurements and a direct determination of the quantities most relevant to neutron dosimetry.

317. AAPM FAST NEUTRON BEAM DOSIMETRY PHYSICS TASK GROUP

Wootton, P., American Assn. of Physicists in Medicine, Division of Medical Radiation Physics, *111 E. Walker Dr., Chicago, Illinois*, 60601, United States of America

The summary for this project is under entry no. 98.

318. AAPM CHARGED PARTICLE DOSIMETRY TASK GROUP

Smith, A. R., Bichsel, H., Lyman, J., Verhey, L., McDonald, J., Lam, K. Y., American Assn. of Physicists in Medicine, *111 E. Walker Dr., Chicago, Illinois*, 60601, United States of America

OBJECTIVES: The primary objectives of this project are: to find solutions to basic physics, dosimetry, and clinical problems in the treatment of cancer with charged particle beams (pions, heavy ions, and protons); to design and build a calorimeter for the absolute calibration of charged particle beams; and to compare charged particle beams of various facilities so that a common dose standard can be developed for the treatment of patient dose at all facilities.

APPROACH: Physicists throughout the world are engaged in this collaborative research effort. They are either already working actively on projects where patients are already being treated with charged particle beams or they are making serious efforts to develop such projects.

PROGRESS: Since all the charged particle therapy facilities were still developing dosimetry systems, techniques, and philosophies, and much basic data were still unavailable, it was determind that it would not be possible to produce a final protocol addressing the above objectives in the first three-year period. Instead, it was decided that a 'state-of-the-art' protocol would be written. Only after additional work can a final protocol be produced.

319. VERIFICATION OF THE VALIDITY OF THERORETICAL MODELS, PARTICULARLY OF COHEN'S MODEL FOR TIME-RELATED DOSE FRACTIONATION

Cavallo, V., David, V., Guerris, R., Marini, M., Porfiri, L. M., Universita degli Studi di Roma, Istituto Radiologia, *c/o Policlinico Umberto I, Rome, Italy*

OBJECTIVE: Verification of the validity of theoretical models, particularly of Cohen's model for time-related dose fractionation.

The purpose of this investigation is the quantitative estimation of opacized lymph node areas in the course of lymphography by means of liposoluble contrast medium. The study was conducted in a group of patients affected by Hodgkin's disease and non-Hodgkin's lymphoma; the control group was composed of patients affected by various diseases and considered negative, in part also during the laparoscopy. On the whole, 1813 normal lymph nodes, 1784 lymph nodes in patients affected by Hodgkin's disease and 1285 lymph nodes in patients affected by lymphoma were examined. Data are being analyzed. However, some preliminary results are available regarding (1) maximum values in cm2; (2) mean values; (3) standard deviation; and (4) meaning of the differences in mean values.

320. CLINICAL TRIALS ON APPLICATION OF TDF FACTORS

Mukherjee, A. K., Ghosh, S., Medical College Hospitals, Dept. of Radiotherapy & Nuclear Medicine, *Chevayoor Kerala, Calcutta 700073, West Bengal, India*

OBJECTIVE: To determine the validity and usefulness of the application of TDF factors in dose calculations with different fractionations and also for split-course radiotherapy.

APPROACH: The patients are being treated with different fractionation schedules and the clinical results are being studied.

PROGRESS: The results are being processed and further trials are being conducted.

321. DEVELOPMENT OF DOSE SCHEDULES TO IMPROVE RADIOTHERAPY OF MALIGNANT TUMORS

Notter, G., Turesson, E. I., Sahlgrenska Sjukhuset, Dept. of Radiotherapy, *S41345 Gothenburg, Sweden*

OBJECTIVE: Biological effects of different fractionation schedules in radiotherapy will be investigated, especially the influence of dose per fraction, treatment time and gap during the radiotherapy course on acute and late effects on normal tissues. The possibilities of multiple daily fractions will also be investigated.

APPROACH: Pig skin and human skin were chosen as the normal tissues to be used in these investigations. For determination of tumor effect, patients with advanced inoperable breast

carcinomas were used. Comparison of the effect of different fractionation schedules was always performed on the same individual for normal tissue as well as for the tumor.

PROGRESS: We intend to evaluate both acute and late effects on normal tissue and local tumor control after different fractionation schedules. Up to now we know the degree of acute reaction to different irradiation techniques but it is necessary to follow up the patients for seveal years to evaluate the late effect. Only a limited number of tumors have been analyzed yet.

322. OPTIMIZATION OF DOSE DISTRIBUTION IN CANCER RADIATION THERAPY

Bjarngard, B. E., Levene, M. B., Paynter, B. H., Berstein, I. A., Bloomer, W., Chaffay, J. T., Chin, L. M., DiGrazia, R., Judy, P. F., Kijewaki, P. K., Larsen, R. D., Leong, J. C., Massachusetts Inst. of Technology, Harvard-M.I.T. Program in Health Sciences & Technology, *77 Massachusetts Ave., Cambridge, Massachusetts,* 02139, United States of America

The broad objective of this research program is to develop methods which will allow the delivery of increased doses of photon beams to the tumor target volume without increasing complications in the normal tissues. This will be achieved by solving key technical problems in radiation therapy that limit the effectiveness of present treatment. Projects in previous years have contributed significantly to the development of the technical capability to deliver a complex treatment plan under computer control with safety and reliability.

The eight proposals in this grant application are oriented toward the following three general areas. The first area includes treatment planning. Projects here involve the selection and modification of diagnostic data for definition of a complex three-dimensional target volume and methods for display and treatment planning utilizing this information. The second general area concerns treatment delivery. Complex tumor target volumes are developed utilizing computer controlled radiation therapy with evaluation of relative merits of different approaches.

Finally, clinical trials of computer controlled radiation therapy will be carried out. Patients will be evaluated both clinically and by physiologic testing to determine the effects of the treatment on normal tissues. The effects of this form of treatment will be compared to those of optimum conventional radiation therapy.

The projects selected will each contribute to an advance in the quality of radiation therapy and will contribute to improved capabilities in optimizing dose to the tumor while minimizing exposure of normal tissues.

323. NON-CONVENTIONAL ADMINISTRATION OF DOSE IN RADIOTHERAPY - CLINICAL & EXPERIMENTAL RESEARCH ON EFFECT OF MULTIPLE DAILY FRACTIONATION

Becciolini, A., Franciolini, F., Balzi, M., Benucci, A., Biagini, C., Cremonini, D., Magrini, S., Nardino, A., Bini, R., Universita degli Studi di Firenze, Istituto Interfacolta di Radiologia, Laboratorio di Radiobiologia, *Viale Morgagni, c/o Policlinico Universitario, 50144 Florence, Italy*

The aim of this research group is to evaluate the effects of non-conventional dose administration such as multiple daily fractionation.

This research is to determine how chronobiological rhythms exert their influence on radiotherapy expecially in order to use non-conventional fractionation of the dose.

The study on multiple daily fractionation was planned to evaluate the radiation responsiveness according to: a) the amount of the single dose fraction, b) the time interval between fractions, c) the hour of the beginning of treatment and then of the circadian phase of the proliferative and differentiated cells, d) the amount of total dose.

The study to concerned with: 1) in man, with regard to the comparison with changes induced by conventional treatments; a) evaluation of biochemical parameters fitted to determine the amount of radiation damage to the organism, b) evaluation of tritiated thymidine uptake of tumor fragments taken from biopsies and cultivated in vitro; 2) in laboratory animals: evaluation, at biochemical, morphological and cellular kinetic levels, of different ways of dose administration in irradiated mammals.

324. STUDIES ON THE DOSIMETRY OF IRREGULARLY SHAPED RADIATION FIELDS

Viswanathan, K. S., Lakshmanan, A. V., Cancer Inst., Dept. of Physics, *Adyar, Madras 600020, Madras, India*

OBJECTIVE: To evaluate dose distribution in irregularly shaped fields.

APPROACH: The modern high energy radiation treatment of Hodgkin's disease uses large fields of about 40 by 40 cm with lead protection for shielding healthy areas of lung and other similar areas. Studies are in progress using an Alderson-Rando tissue-equivalent phantom and LiF-100 thermoluminescent dosimeter. A special geometric cutting machine has been designed to cut out the irregular field in thermal sheath material. A low melting alloy (Bi, Cd, Sn and Pb) with a melting point of 80 degrees C is employed to make a radiation shield for the individual patient.

325. REAL-TIME RADIOTHERAPY TREATMENT MONITOR

Padikal, T. N., Fraass, B. A., Roberson, P. L., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Radiation Physics & Computer Automation Section, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

The purpose of the project is to develop a real-time monitor for radiation treatments. Although routine quality assurance is the immediate aim, continued development will make feasible many projects which rely on real-time patient dose monitoring.

326. BIOLOGIC EFFECT OF FRACTIONATED RADIOTHERAPY FOR LARYNGEAL CANCER

Hansen, H. S., Hjelm Hansen, M., Sorensen, P. B., Finseninstitutet, Radium Centre, *Strandboulevarden 49, DK2100 Copenhagen, Denmark*

OBJECTIVE: The aim is to identify the dose-response curves valid for fractionated radiotherapy in treatment of laryngeal carcinoma. Dose may be the physical absorbed dose or any measure of the biologic effect of the given treatment, estimated by use of mathematical models combining the effect of absorbed dose, fractions, time, tumor size and field size. Dose-response curves for tumors as well as for normal tissues will be determined.

APPROACH: The radiotherapy schedule that is utilized will be recorded in detail in a computer and all existing fractionation models will be used in order to obtain estimates of the biological effective dose.

Clinical findings - especially such as residual tumor/local recurrence, lymph node metastases, death and complications after irradiation and/or secondary surgery will be recorded and the frequency of these events calculated as functions of the different measures of biologic dose in order to construct the dose-response curves.

PROGRESS: It is already known from literature and from similar studies in Denmark that dose-response curves do in fact exist. It is also known from a pilot study that dose-response is to be expected in the present material. By combining the data it is hoped that dose-response curves may be found with sufficient accuracy to allow an optimization of the treatment.

327. RADIOBIOLOGICAL INVESTIGATIONS OF FRACTIONATION PROBLEMS OF RADIOTHERAPY OF MALIGNANT TUMORS

Littbrand, B., Midander, J., Karolinska Institutet, Dept. of Tumour Biology, *Solnavagen 1, S10401 Stockholm 60, Sweden*

Different factors important for radiotherapy are investigated in vitro; for instance the effect of oxygen on the lethal effect of radiation and repair of damage, radiosensitizer and cytostatics used in the clinic. A clinical trial based on these results is proceeding with superfractionated treatment of bladder carcinoma. The clinical results are encouraging.

328. CLINICAL EVALUATION OF EFFECTS OF DIFFERENT FRACTIONATION REGIMES IN RADIOTHERAPY

Loasses, A., Banelli, E., Capua, A., Maurizi Enrici, E., Salsano, F., Tombolini, V., Vitturini, A., Universita degli Studi di Roma, Istituto Radiologia, *c/o Policlinico Umberto I, Rome, Italy*

(a) Cell-mediated immunitary implications of a two-fraction scheme of post-surgical radiotherapy in patients affected by breast cancer: 67 patients were treated from December 1976 to April 1979. Average age was 51; 83 percent were resected following the method of Halsted; stage percentages: I 6, II 51, III 43. Technique of treatment: irradiation of regional lymph nodes by a shielded direct field, 4 MeV x-rays, produced by Linac. A depth dose of 1800 rads was reached in two sucessive fractions of 900 rads each, separated by a 48-hour interval. The treatment was well-tolerated and symptomatic side-effects were minimal. Follow-up is in progress. Four cases of relapse in the non-irradiated chest wall were observed. Analysis of the time course of peripheral blood cells appears to show a very limited drop in lymphocytes and in granulocytes. An immunologic evaluation is in progress.

(b) Split-course versus continuous radiotherapy for carcinoma of the uterine cervix: The aim is to compare the effects of continuous versus split-course scheme of irradiation for stage III or II squamous cell carcinoma of the uterine cervix, by a randomized study. End-points are response/remission rate, morbidity of treatments, and survival rate. Dosage schedule: Arm A: continuous radiotherapy - 4000 rads in 5 weeks by 4 MeV Linac x-rays, followed by intracavitary treatment with Ir-192. Arm B: split-course scheme: two fractions 850 rads each, 4 MeV Linac x-rays, separated by a 48-hour interval, followed by intracavitary treatment with Ir-192 after three weeks. Sixteen patients have been entered (12 in arm A, 4 in arm B). Split-course therapy was well tolerated by all 4 patients who showed complete remission. Six of twelve patients treated by conventional fractionation showed partial remission, and three of six after full remission developed a central relapse.

329. RADIOTHERAPEUTIC CONTROL - COMPARISON OF DIFFERENT TYPES OF FRACTIONATED DOSES IN DIFFERENT NEOPLASMS

Pescetto, G., Ragni, N., Caldana, P. L., Bentivoglio, G., Scarpati, D., Pilot, A., Universita degli Studi di Genova, Obstetrics & Gynecology Unit, *Viale Benedetto XV, 2, 116132 Genoa, Italy*

OBJECTIVES: Evaluation of cesiotherapy in the course of cervical and vaginal therapy and in the prevention and therapy of vaginal recurrences of endometrial and cervical cancers; demonstration of possible advantages in the treatment of some gynecological neoplasms with fractionated doses; evaluation of the collateral effects of cesiotherapy; follow-up of the patients treated and computerized analysis of the data obtained for the evaluation of the effects of different types of cesiotherapeutic treatment and of different radiosurgical combinations.

APPROACH: 1) Treatment of 17 cases of cervical cancer, 7 of whom will be treated with fractionated cesiotherapy before surgical treatment and the remaining 10 (5 plus 5) - with 2 different sources with different intensity of doses, using the two stocks of sources provided by 'Curietron.' 2) Treatment of 10 cases of endometrial cancer with intracavitary cesiotherapy before surgical treatement, 5 of whom will be treated with a single dose and the other 5 - with fractionated doses, followed by surgical treatment after 4 weeks. It will be possible to establish which treatment has the greatest chances of therapeutic success, with clinical and physical controls (lymphography, ultrasound, TAC). 3) A two-year treatment of 10 cases of vaginal cancer, 5 of whom will be treated with a single dose of cesiotherapy and 5 with fractionated cesiotherapy. A follow-up using clinical and bioptical controls for all the patients treated with this type of therapy is planned.

330. MEASUREMENT OF EARLY AND LATE NORMAL TISSUE TOLERANCE TO FRACTIONATED THERAPEUTIC X-IRRADIATION

Wiernik, G., Hopewell, J. W., Yeung, T. K., Young, C. M., Foster, J. L., University of Oxford, Research Inst., *c/o Churchill Hospital, Oxford, England, United Kingdom*

OBJECTIVE: To establish tolerance levels for acute and late radiation damage in skin for a variety of clinically applicable fractionation regimes.

APPROACH: Three functional end points are being evaluated: 1) By the quantitative assessment of early and late skin reactions by scoring erythema, pigmentation, desquamation, contracture and necrosis. Results are analyzed using non-parametric statistical tests. 2) By skin blood flow estimations using the intra-dermal injection of 99mTc. Simultaneous measurements are made of relative isotope clearance from an irradiated and from a control site. 3) By measuring the relative survival length of irradiated and control skin flaps raised as pedicle skin grafts. For direct comparison with these studies of function we are applying morphometric methods of analysis to histological sections of skin to identify the causes, at the cellular level, which give rise to the functional changes.

PROGRESS: We have identified two distinct waves of tissue response. The first appears to be related to the epithelial cell population. Severe acute damage results in moist desquamation which will heal provided the dose was within tissue tolerance. A second wave reaction follows which has been shown to be associated with a dose of dependent reduction in blood flow. When the blood flow is very severely impaired an early dermal necrosis will result 12-16 weeks after treatment. When treatment is given in a small number of individually large fractions, dermal necrosis may occur without prior epithelial desquamation. The reduction in blood flow at 3 months following irradiation occurs before, and may result in, the development of field contraction. The severity of linear field contraction has been used to derive dose response curves for late radiation damage in the skin for a range of fractionation regimes. Time and fractionation factors have been derived for equivalent levels of late damage (Hopewell, Foster, Young and Wiernik. 1979, Radiology 130, 783-788).

VI. BROAD CANCER RADIOTHERAPY PROGRAMS

A. CLINICAL RESEARCH PROGRAMS AND CENTERS

331. RADIATION THERAPY AND BIOLOGY RESEARCH PROGRAM

Fischer, J. J., Yale University, School of Medicine, Dept. of Therapeutic Radiology, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

Clinical studies in advanced carcinoma of the head and neck region, Hodgkin's disease and non-Hodgkin's lymphomas, carcinoma of the breast, gastrointestinal cancer, gynecologic malignancies, prostatic cancer and radiation dose rate effects on the hematopoietic system are continued and new studies are planned.

Radiological physics research includes: magnetic control of the dose distributions produced by high energy electron beams, calorimetric determination of dosimetric parameters and general medical physics.

Laboratory investigations include: experimental radiation therapy of rodent solid tumors, radiation reaction preventive agents and normal tissue response, the response of vascular endothelium to ionizing radiation, NMR detection of hypoxic cells, the influence of the red blood cell concentration of 2,3-diphosphoglycerate on the radiation response of the rat rhabdomyosarcoma R1112.

Our investigations also include: enzymatic mechanisms in postreplication repair; study of error-prone DNA repair pathways in mammalian cells, study of herpes virus genome structure, site specific mutagenesis in gene for thymidine kinase of herpes simplex virus; molecular mechanisms of DNA repair in E. coli, hypoxic radiosensitizers: structure-function relations and mechanisms of sensitization and toxicity; analysis of gene function involved in genetic recombination in E. coli; site directed mutagenesis, role of secondary structure in gene regulation; cell proliferation in EMT6 tumors and examination of new agents for altering the radiation response of solid tumors.

332. RADIATION THERAPY ONCOLOGY PROGRAM

Maruyama, Y., University of Kentucky, School of Medicine, Dept. of Radiation Medicine, *Limestone & Euclid, Lexington, Kentucky*, 40506, United States of America

The aim of the research to be conducted under the proposed program is directed toward a better understanding of basic radiation and tumor biology with single cell systems, animal and tumor systems, tumor detection and staging research and applied research in human cancer and radiotherapeutic

problems. The Radiation Oncology Program utilizes the patient population of this region for study. Attempts will be made to coordinate and combine the efforts of the laboratory with those of the clinic. We will conduct long-term multi-disciplinary programs in cancer treatment as well as cancer biomedical research, both applied and fundamental. This program's goals are to develop through research and investigative efforts, means to cure patients who develop cancer, to provide maximum palliation to patients not cured, to control the progress of disease and to assess the extent and localization of lesions by isotopic diagnostic tests.

333. PARTICLE PROGRAM - CLINICAL TRIALS

Kramer, S., Davis, L. W., Zelen, M., Hanley, J., American College of Radiology, Dept. of Radiation Therapy, *6900 Wisconsin Ave., Chevy Chase, Maryland*, 20015, United States of America

There are currently five (5) funded neutron facilities, one pi-meson facility and one heavy ion facility that are in the process of initiating random allocation clinical studies. It is proposed that these studies be developed and controlled under the auspices of the Radiation Oncology Study Center. It is projected that approximately 1,000 study patients per year will be accessed by the particle users both to randomized and non-randomized studies.

The Radiation Oncology Study Center will be supplying the following services: (1) Develop the discipline necessary for group studies. (2) Develop the mechanism and assist in the monitoring of medical quality control for the control patients in the networks. (3) Assist in protocol development. (4) Assist in forms development. (5) Serve as a focus for data capture for the group. (6) Provide data analysis for the group.

334. COMMUNITY RADIATION ONCOLOGY PROGRAM

George, F. W., University of Southern California, School of Medicine, Dept. of Radiology, *2025 Zonal Ave., Los Angeles, California*, 90033, United States of America

The Community Radiation Oncology Program (CROP) is a community outreach program of USC Comprehensive Cancer Center that has as its objective the development and implementation of an intergrated program of activities that provide rapid translation of recent advances in oncology to the management of cancer patients using the radiation oncologist as a viable focus for implementing the program in individual institutions. It is conducted on the basis that the radiation therapist, as a full-time oncologist, is a natural resource for intergrating the development of cancer control activities in community settings, through which not only the radiation oncologists but other specialities and disciplines are brought into the process of improving cancer control. The objectives are accomplished through activities that increase the skills, knowledge, and capabilities of the radiation therapy community (including physicians, nurses, physicists and technologists), and bring together radiation therapists and other specialties and disciplines in multi-disciplinary cancer management efforts.

335. MULTIDISCIPLINARY PROGRAM IN RADIATION ONCOLOGY

Wirtanen, G. W., University of Wisconsin, Madison Campus, Medical School, Dept. of Human Oncology, *450 N. Randall Ave., Madison, Wisconsin*, 53706, United States of America

The objectives of this proposal from the Division of Radiation Oncology, Department of Human Oncology, at the University of Wisconsin Clinical Science Center are: 1. To continue clinical studies in radiation therapy with emphasis on tumor localization, treatment planning and quality control, normal tissue tolerance, and therapy with combined modalities (including hyperthermia and/or intra-arterial chemotherapy). 2. To continue preclinical research to include biologic effects of combined modality therapy (especially on normal tissues), the carcinogenic aspects of ionizing radiations, the effects of microwave and water bath hyperthermia (with or without ionizing irradiation) on membranes, cells, and tissues, and mechanisms of in situ repair. 3. To continue research on the dosimetry of high energy electrons and photons, and improve high energy electron beam dose distribution with magnetic fields. 4. To develop ultrasound and CT to improve tumor detection and margin delineation, and develop practical methods for using CT information for treatment planning. 5. To develop suitable tumor-localizing radiopharmaceuticals for improved detection and definition of tumors and for predicting responses to cytotoxic therapy. To use nuclear medicine and special computerized tomography techniques for the evaluation of dynamic physiologic changes which occur in tumors and normal tissue following irradiation or therapy with cytotoxic drugs, particularly adriamycin and 5-FU. 6. To provide excellent training in radiation therapy, radiation biology, and radiation physics at the predoctoral and postdoctoral level. 7. To promote optimal use of radiation therapy as part of a multidisciplined approach to the treatment of cancer within the U.W. Clinical Sciences Center and the Wisconsin Clinical Cancer Center.

336. IMPROVEMENTS IN RADIATION THERAPY TREATMENT PLANNING

Hendee, W. R., Cacak, R. K., Paquette, F. R., University of Colorado, Health Sciences Center, School of Medicine, Dept. of Radiology, *4200 E. 9th Ave., Denver, Colorado*, 80262, United States of America

The principal objective of this project is to develop a computer-based radiation therapy treatment planning program that accounts for tissue heterogeneities and accurately (within plus or minus 5%) computes the dose delivered to patients treated with 6-18 MeV electrons. The program will use computed tomographic data to predict the location, configuration and absorption characteristics of anatomical features of patients being treated. The influence of these features on the absorption and scattering of electrons will be estimated analytically and verified experimentally, leading to development of an algorithm for calculating dose distributions for electron treatments. Calculated dose distributions will be compared to actual dose distributions measured in phantoms to estimate the accuracy of the algorithm in a variety of patient geometries.

337. RADIOBIOLOGICAL TECHNIQUES IN HUMAN CANCER THERAPY

Mendelsohn, M. L., Gray, J. W., Pallavicini, M., Dean, P. N., Moore, D., George, Y., Folstad, L., University of California, Central Office, Lawrence Livermore Lab., Biomedical Sciences Division, *P.O. Box 808, Livermore, California*, 94550, United States of America

Our objective is to develop and apply suitable methods of cell cycle analysis with which the growth kinetics of cancer and normal cells from man and experimental animals can be understood in the context of cancer therapy with drugs and radiation. We are especially interested in flow cytometric methods of kinetic analysis because they offer the promise of powerful, sensitive, rapid and practical approaches to kinetic analysis under steady-state and in the midst of therapy. We are continuing kinetic technique development in vitro using Lewis Lung (LL) tumor cells, KHT tumor cells and a dual Chinese hamster ovary (diploid plus tetraploid cultures) cell system. Emphasis is currently on the response of these cells to multiple doses of cell cycle phase specific drugs such as cytosine arabinoside (ara-C), hydroxyurea (HU) and vincristine (VCR). As kinetic techniques are developed in vitro, they are applied to kinetic studies of the response of LL and KHT tumors in vivo. We are also developing high pressure liquid chromatographic techniques for the measurement of levels of drugs and drug metabolites during therapy for correlation with the cell cycle kinetic effects. Extensive computer programs are being developed for the analysis of our cell cycle and pharmacokinetic data.

BIBLIOGRAPHIC REFERENCES: Nakeff, A., Valeriote, F., Gray, J.W., Grabske, R.: (1979) Application of Flow Cytometry and Cell Sorting to Megakaryocytopoiesis. Blood 53, 732-745. Gray, J.W., Dean, P.N., Mendelsohn, M.L.: (1979) Cell Cycle Analysis by Flow Cytometry and Sorting. In: Flow Cytometry and Sorting, (M. Melamed, P. Mullaney, M. Mendelsohn, eds.) John Wiley and Sons, New York, pp.383-407.

338. CLINICAL AND RESEARCH RADIATION THERAPY IN CANCER CARE

Kramer, S., American College of Radiology, *925 Chestnut St., Philadelphia, Pennsylvania*, 19107, United States of America

This proposal requests a supplement to the recommended level of funding for the patterns of care study in its sixth year. Approval of this proposal would essentially continue funding at the level already provided for the fifth year. We specifically request continuation of support for the following programs:

Multi-disciplinary approaches, education, utilization of professional personnel and referral patterns, and survey. These programs form vital components of the total PCS effort.

The multi-disciplinary program of the patterns of care study proposes to mount a joint study with the College of American Pathologists to determine the feasibility of a nationwide quality control review of pathology records. We continue to communicate with other oncologic specialists concerning possible similar reviews in their disciplines.

In the area of education, substantial progress has been made as the PCS findings have become clear. The educational program is extremely important because it is the chief means to communicate these findings to the medical community.

In utilization of professional personnel and referral patterns, it has proven difficult to quantify, for analytical purposes, the effects of the environment in which radiation therapy is practiced. Yet, knowledge of such effects promises a major impact on our future efforts.

In the area of survey, we plan, during the coming year, a survey of institutions to augment our outcome data base and thereby increase the efficiency of our analytical efforts. We plan also to survey selected institutions to evaluate the effectiveness of other PCS programs.

In addition to these programs, we will naturally be continuing all other aspects of the study which have been recommended for funding.

339. MODELS IN RADIATION ONCOLOGY

Cohen, L., University of Chicago, Michael Reese Hospital & Medical Center, Dept. of Radiation Oncology, *2929 S. Ellis Ave., Chicago, Illinois*, 60616, United States of America

Effective radiotherapy implies progressive depletion of the cancer cell population during treatment with concomitant repopulation of the normal tissues. In the belief that further improvement of the results of radiation therapy could result from a fuller understanding of underlying radiobiological mechanisms, an algorithm for simulating the changes in the cell populations of both normal tissues and tumors during fractionated irradiation has been developed and tested in the clinical context. The results obtained with a number of practical applications of this program have been widely published. It is not normally possible however, to publish full listings and users' instructions for each of the programs employed. This proposal is designed to rectify this eficiency.

The proposed monograph will describe methods for clinical evaluation of dose-time-volume relationships, radiation quality, fractionation, overall time, and field size as well as specific parameters for repair, recovery and repopulation; methods for computer simulation of changing cell populations in irradiated tissues and tumors together with algorithms for derivation of parameters; it will provide documentation relating to the programs used.

340. SERVICE CLINICAL RADIATION PHYSICS

Padikal, T. N., Roberson, P. L., Fraass, B. A., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Radiation Physics & Computer Automation Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

OBJECTIVE: Provide expert consultations in Radiation Physics, radiotherapy treatment planning and calibration services of accelerators for purposes of treatment of clinical center patients admitted for services in the Radiation Oncology Branch of the National Cancer Institute. The Branch now has the capability of treating with a 10 MV photon beam.

341. RADIATION PHYSICS - NEOPLASM TREATMENT PLANNING AND DOSIMETRY (HUMAN)

Rubin, P., University of Rochester, School of Medicine & Dentistry, Dept. of Medicine/Radiology/Surgery, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

This is part of a broader project. A summary of this subproject is not available.

342. CLINICAL RADIOTHERAPY CORE

Fletcher, G. H., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Radiotherapy, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

This is part of a broader project. A summary of this subproject is not available.

343. RADIATION THERAPY CORE

Fischer, J. J., Yale University, School of Medicine, Dept. of Therapeutic Radiology, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

This is part of a broader project. A summary of this subproject is not available.

344. RADIATION ONCOLOGY STUDIES (HUMAN)

Ubinas, J., University of Puerto Rico, Medical Sciences Campus, School of Medicine, Dept. of Radiation Therapy, *P.O. Box 5067, Rio Piedras*, 00936, Puerto Rico

This is part of a broader project. A summary of this subproject is not available.

345. RADIATION THERAPY (HUMAN)

Owens, A. H., Johns Hopkins University, School of Medicine, Dept. of Medicine, *725 N. Wolfe St., Baltimore, Maryland*, 21205, United States of America

This is part of a broader project. A summary of this subproject is not available.

346. CLINICAL RADIATION ONCOLOGY (HUMAN, MICE)

Parker, R. G., University of Washington, School of Medicine, Dept. of Radiology, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington*, 98195, United States of America

This is part of a broader project. A summary of this subproject is not available.

347. WHOLE BODY IRRADIATION

Peters, L., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Radiotherapy, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

This is part of a broader project. A summary of this subproject is not available.

348. RADIATION AND DRUG SENSITIVITY

Durand, R. E., Johns Hopkins University, School of Medicine, Dept. of Radiation Oncology, *725 N. Wolfe St., Baltimore, Maryland*, 21205, United States of America

This is part of a broader project. A summary of this subproject is not available.

349. EXPERIMENTAL CLINICAL RADIATION ONCOLOGY

Levitt, S. H., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Therapeutic Radiology, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

This is part of a broader project. A summary of this subproject is not available.

350. RADIOTHERAPY OF CANCER PATIENTS

Ghossein, N. A., Yeshiva University, Bronx Campus, Albert Einstein School of Medicine, Dept. of Cell Biology, *1300 Morris Park Ave., Bronx, New York*, 10461, United States of America

This is part of a broader project. A summary of this subproject is not available.

351. CANCER RADIOTHERAPY

Rubin, P., University of Rochester, School of Medicine & Dentistry, Dept. of Pathology, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

This is part of a broader project. A summary of this subproject is not available.

352. RADIOLOGICAL PHYSICS CENTER

Shalek, R. J., Hanson, W. F., Gagnon, W. F., Berkley, L. W., Givens, S. B., Kirby, T. H., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Physics, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

The Radiological Physics Center (RPC) was established upon the recommendation of the Committee on Radiation Therapy Studies (CRTS), now the committee on Radiation Oncology Studies (CROS), under the sponsorship of the American Association of Physicists in Medicine (AAPM) to insure the

correctness and consistency of radiation dosimetry among institutions involved in interinstitutional clinical trials. Review of dosimetry is accomplished by visits to institutions by a physicist, irradiation of various mail-out dosimeters, and by review of dosimetry on patients entered into clinical trials. When errors are discovered, the RPC cooperates with the institution to rectify the errors. To date there are 15 active clinical study groups and 4 intergroup efforts served by the RPC. The RPC is presently reviewing individual patient records for patients entered onto 54 active protocols. Numerous protocols are in planning stages. Visits have been made to 254 institutions. Dosimetry discrepancies have been found at 98 institutions of which 88 have been resolved. The review of brachytherapy calibration and dosimetry calculation has begun. Measurement of brachytherapy calibrations has been done at 27 institutions. Efforts are made to develop calculative methods and efficient techniques for measurements that are important to clinical trials. Experience gained in developing quality control procedures for one clinical trial is communicated to other clinical trial groups. This information and other knowledge gained are communicated to the radiological community.

BIBLIOGRAPHIC REFERENCES: L. W. Berkley, W.F. Hanson and R.J. Shalek: Discussion of the Results of Measurements with a Portable Well Ionization Chamber for Calibration of Brachytherapy Sources, Proceedings of the 1979 Workshop: Recent Advances in Brachytherapy Physics, New England Chapter of the American Association of Physicists in Medicine, October 5-6, 1979. in press.

353. CANCER CONTROL RADIOLOGIC PHYSICS CENTERS

Laughlin, J. S., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

The overall objective is to significantly improve the quality of radiation treatment and diagnosis in the Cancer Control projects throughout a determined network of hospitals within an assigned region of the country. Further, the Contractor will establish a mechanism for performing intercomparisons with other Radiologic Physics Centers to assure that the standards for all the participating network institutions throughout the nation are similar and of the same high quality.

354. RADIATION THERAPY CLINICAL AND RESEARCH CENTER

Brady, L. W., Hahnemann Medical College & Hospital, Medical College, Dept. of Radiation Therapy & Nuclear Medicine, *235 N. 15th St., Philadelphia, Pennsylvania*, 19102, United States of America

Five years ago, the Hahnemann Medical College and Hospital was designated as a Radiation Therapy Center. Since that time - thanks to funding from the Center Grant and other sources - considerable progress has been made. Funding of the current continuation application will enable the Center to progress further in bringing together those disciplines dealing with cancer, thereby producing optimum conditions for cancer clinical research, service to patients, basic cancer research, and training of physicians and paramedical personnel for cancer research and treatment. Major needs of the Center consist of more nearly adequate facilities and equipment for research assignments as well as basic science, administrative and clinical personnel to facilitate the research program.

355. RESEARCH AND CLINICAL RADIATION THERAPY CENTER

Kramer, S., Thomas Jefferson University, Jefferson Medical College, Dept. of Radiation Therapy & Nuclear Medicine, *1025 Walnut St., Philadelphia, Pennsylvania*, 19107, United States of America

Support is requested for an expanded multi-disciplinary integrated program of cancer research including studies of: (a) Cell and tissue response to hyperthermia, combinations of drugs and radiation, as well as environmental and other agents. (b) Physics and dosimetry of high energy photons, electrons and neutrons as well as treatment optimization with computer assisted tomography, ultrasound and computer treatment planning. (c) Clinical trials of aggressive radiation therapy based on observations and information from these and other scientific studies and clinical observations. (d) Assessment of the quality of life and function and late effects of long-term survivors after definitive radiation therapy. (e) Development of cancer patient information system for quality control of care and for research into clinical success and failure.

Emphasis will be placed on inter-disciplinary and inter-departmental exchange of information and understanding as well as clinical care and teaching.

356. RADIATION ONCOLOGY RESEARCH AND CLINICAL CENTER

Levitt, S. H., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Therapeutic Radiology, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

The overall objective of this program project is to explore and improve the utilization of radiation and combinations of radiation and other modalities in order to increase the cancer cure rate and to evaluate the long-term effects of radiation and combinations of radiation and other modalities; thus, not only to increase the cure rate but preserve function and cosmesis in the cancer patient.

These objectives will be achieved by: a. Continuing the development of a specialized Radiation-Oncology Research and Clinical Center. This Center will continue to develop an overall integrated program for research in radiation biology, radiation immunology, radiation physics and related basic sciences and continue to promote, enhance and stimulate the investigation of the basic mechanisms of radiation and combinations of radiation and other agents in the treatment and control of cancer and evaluation of long-term effect with the goal of possible human application. b. Continuing to expand our overall integrated program to carry out clinical research utilizing radiation combined with other agents to improve results of the treatment of human cancer and to integrate information obtained from basic research whenever possible into the clinical treatment. c. Continuing to provide a center for demonstration and teaching of the appropriate advanced therapeutic methods and techniques so that these can be taught to physicians, medical students, and support personnel of this area and thus be made available to patients. d. Continuing to provide and further develop our Training Program in radiation oncology for graduate and undergraduate physicians, technicians, and nurses for this region. e. Continuing our development of the Outreach Program to improve radiation therapy and subsequently all methods of cancer treatment in the outlying communities of the region.

357. RADIOTHERAPY ONCOLOGY CENTER

Wallach, D. F., Curran, B., Emami, B., Hughes, W. L., Beth, E., Tufts University, Boston Campus, New England Medical Center Hospital, Dept. of Therapeutic Radiology, *171 Harrison Ave., Boston, Massachusetts*, 02111, United States of America

The overall objective of the Radiotherapy Oncology Center (program project) of the Department of Therapeutic Radiology at Tufts-New England Medical Center remains the continuation and development of coordinated, interdisciplinary research designed to improve knowledge and techniques and develop therapeutic approaches for the optimization of cancer treatment by radiation and adjunctive therapy. Thermal manipulation in the treatment strategy is the major adjunct proposed for investigation -from the genetic, biochemical, biophysical, immunological, cellular, physiological, and clinical points of approach. Other proposals will investigate radiosensitization, radioprotection, tumor tissue perfusion and beam/dosimetry optimization. The projects involve basic molecular science, cellular and animal studies, and clinical investigations by tumor and radiation biologists, physicists, and clinicians, with intentional involvement of investigators on several individual projects and interrelations among projects; all of which is designed to foster a unified multidisciplinary approach to the goals of the Radiotherapy Oncology Center (program project).

BIBLIOGRAPHIC REFERENCES: R. Schmidt-Ullrich, S.J. Kahn, W.S. Thompson and D.F.H. Wallach (1980) Host cell-modified T antigen in membranes of simian virus 40 (SV40)-transformed cells. J. Natl. Cancer Inst., (in press). R. Schmidt-Ullrich and D.F.H. Wallach (1980) Papovavirus-specific surface membrane antigens of cells transformed by simian virus 40 and BK virus, in Oncogenic viruses and human cancer (G. Giraldo and G. Tarro, eds.) Academic Press, N.Y. in press.

358. CLINICAL RADIATION RESEARCH CENTER

Rubin, P., Sutherland, R., Smathers, J. B., Keys, H., Salazar, O., Keller, B., Graves, R., Conroy, P., University of Rochester, School of Medicine & Dentistry, Dept. of Radiology/Medicine/Surgery, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

The intellectual integration of the various sections into a coherent yet individualistic scientific research program relates strongly to a carefully selected set of major scientific themes. These research programs constitute the major investigative activities of the Division of Radiation Oncology and the CRRC and rely heavily on and utilize the laboratory to model and simulate clinical problems and through such laboratory efforts, to better understand the pathophysiological effects of radiation in humans with malignant disease. The major research themes are the combined modality experimental and clinical therapeutic programs, radiation toxicology and pathology, radiosensitizers and hyperthermia and clinical cooperative group activities. The radiobiology and biophysics programs, through the investigation of the spheroid or tumor models, allow for combination of some of the radiation innovations referred to in a scientific approach to combine modalities. Once promising results emerge from the laboratory experience, pilot studies can be introduced and implemented in our hospital through collaboration of radiation oncology and medical oncology. Special clinics, oncology beds, nursing oncology support, social and psychiatric workers are available. The radiation physics program provides special support for the other programs, but has its own research and development programs in developing guidelines for precise dosimetry, quality control of treatment plans and hopes to conduct research in high LET radiation.

B. RADIATION THERAPY PROTOCOLS

359. HODGKIN'S DISEASE, STAGE IIB, IIE, IIS, IIIA, IIIB (AGE 15-65 YEARS) CONTROLLED STUDY OF COMBINED TREATMENT - CHEMOTHERAPY AND RADIOTHERAPY

Barfi, A., Biasi, Buraggi, Guindani, Pagnoni, Recchione, Rodari, Santoro, Spinelli, Villani, Volterrani, Zucali, Istituto Nazionale per lo Studio e la Cura dei Tumori, *1 Via G Venezian, 20133 Milan, Italy*

OBJECTIVE: Hodgkin's disease, stage IIB, IIE, IIS, IIIA, IIIB - a) Comparative evaluation of the effectiveness of two combined treatments: 1) 3 cycles MOPP plus RT plus 3 cycles MOPP; 2) 3 cycles ABVD plus RT plus 3 cycles ABVD. b) Systematic evaluation of the possible iatrogenic damage to the following organs: gonads, lung, heart and pericardium, thyroid, kidney, salivary glands, bone marrow.

APPROACH: Age of eligible patients - 15-65 years. Patients are stratified according to the following parameters: stage, modalities of staging, and histologic subtype. The patients are then randomized to treatment 1 or 2. For the alleviation of iatrogenic damage clinical tests are performed before the beginning of treatment, after the first three cycles of CT, at the end of RT, at the completion of the whole treatment and during the following three years, at 6-month intervals.

PROGRESS: Thirty-four patients were entered on the two combined treatment protocols according to the protocol. Only 16 were submitted to clinical tests for the alleviation of the iatrogenic damage.

360. NO. 7551 - COMBINATION CHEMOTHERAPY AND RADIOTHERAPY FOR STAGE IV HODGKIN'S DISEASE, NO PRIOR TREATMENT

Spaulding, M. B., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

This study compares combination chemotherapy with CCNU, vinblastine, procarbazine and prednisone given continuously with the combination drugs given with radiation therapy in patients who present primarily with advanced Stage IV Hodgkin's disease. The study is continuing. One patient has been entered at the VA Medical Center. The patient tolerated the treatment well. However, relapse occurred after three courses of chemotherapy. This patient has subsequently received radiation alone and remains free of disease. Final results are not available as this is part of a larger study.

361. NO. 7751 - POOR RISK PATIENTS, STAGE I AND II HODGKIN'S DISEASE

Spaulding, M. B., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

This study is designed to determine if involved field radiotherapy plus six cycles of chemotherapy with CCNU, Velban, procarbazine and prednisone prolongs the total duration of remission as compared to combination chemotherapy alone in patients with poor prognosis Hodgkin's disease. It will also determine whether combination chemotherapy alone, as compared to involved field radiotherapy, significantly decreases the morbidity or mortality and whether disease relapse patterns (either inside or outside irradiated fields) are different. This is part of a larger study and no results are available at this time.

No patients have been entered on this study.

362. CALGB PROTOCOL 7451 - STAGE III HODGKIN'S DISEASE

Spaulding, M. B., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

This study is designed to determine if combination induction chemotherapy followed by single agent maintenance produces different frequencies of response and durations of remission and survival compared to total nodal radiation alone, total nodal radiation followed by chemotherapy or chemotherapy followed by total nodal radiation. No patients have been entered from the VA. This is part of a larger study and there are no results available at this time.

363. PROTOCOL FOR STAGING AND TREATMENT OF NON-HODGKIN'S LYMPHOMAS

Kaplan, R. S., Wiernik, P. H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Oncology Branch, *Baltimore, Maryland*, 21201, United States of America

At the time of presentation, non-Hodgkin's lymphomas are frequently disseminated. There exist, however, a number of patients wth localized disease following completion of all clinical and pathologic staging. It is in this group of patients that radiotherapy is most useful. However, the question of whether adjuvant chemotherapy following radiation therapy is of any benefit is as yet unanswered. Patients who are found to have pathologically Stage I and II non-Hodgkin's lymphomas following a variety of staging procedures including staging laparotomy were randomized to receive either extended field irradiation alone, or extended field irradiation followed by six courses of chemotherapy using Cytoxan, vincristine and prednisone. Fifteen patients whose staging laparotomies were entirely negative have been randomized to one or the other of the treatment arms. Analysis of staging data is underway. No conclusion can be drawn as yet as to the value of adjuvant chemotherapy.

BIBLIOGRAPHIC REFERENCES: Diggs, C.H., Wiernik, P.H. and Ostrow, S.S.: Modular Lymphoma: Prolongation of Survival by Complete Remission. Cancer Clinical Trials (In press) 1980. DeVita, V.T., Glatstein, E.J., Young, R.C., Hubbard, S.M., Simon, R.M., Ziegler, J.L. and Wiernik, P.H.: Changing Concepts: The Lymphomas. In Jones, S.E. and Salmon, S.E. (Eds). Adjuvant Therapy of Cancer II, Grune and Stratton, New York 1979, pp 179-190.

364. PROTOCOL OF TREATMENT FOR RHABDOMYOSARCOMAS USING SURGERY, RADIATION THERAPY AND CHEMOTHERAPY - PHASE III

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OBJECTIVE: To determine the usefulness of treatment consisting of surgery, radiation therapy and chemotherapy in relation to stage of disease.

APPROACH: Surgery for extirpating and evaluating extension of tumor. In total extirpation, use of radiation therapy. In partially resectable tumors, use of radiation therapy and chemotherapy (cyclophosphamide, vincristine, actinomycin D and adriamycin. Use of irradiation on distal metastases. This is a controlled trial.

PROGRESS: Twenty-five patients under study. (Translated)

365. A PROTOCOL TO STUDY MULTIPLE SYMPTOMATIC OSSEOUS METASTASES WITH SEVERAL DOSES OF HALF-BODY IRRADIATION

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OBJECTIVES: To evaluate the frequency and the duration of pain relief as a function of the dose schedules proposed. To assess tumor and response by evaluation of measurable lesions in different sites. To determine the normal tissue tolerance and toxicity following single exposure doses of irradiation, particularly focusing on the dose-limiting organs: bone marrow, lung, kidney, brain, spinal cord, small bowel and heart, in terms both of acute and late reactions and of damage. To further study the natural history of progression of disseminated cancer, particularly the osseous lesions, and to develop a useful staging system for evaluation of disseminated disease.

Treatment options are divided into two categories (upper half of the body and lower half of the body). The investigator will select which half of the body is more involved and deserves immediate treatment. (1) Multiple Bone Metastases in the Upper Half of the Body. Irradiation of the upper half of the body with 600, 700, or 800 rad single dose. This includes the top of the naval or iliac crest to the top of the skull. It requires correction of dose for lung transmission. It also requires a 24 hour hospitalization and a pre-medication program. (2) Patients with Multiple Bone Metastases in the Lower Half or Middle Segment of the Body. Radiation to the half of the body with 800, 900, or 1000 rad single dose. This does not require correction of dose, hospitalization, or pre-medication other than antiemetics.

366. BRAIN TUMOR PROTOCOL 77-02 - SURGERY, RADIATION THERAPY, BCNU, RADIATION SENSITIZER, AND STREPTOZOTOCIN

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The purpose of this study is to determine, in a patient population with known malignant glioma who have undergone cytoreductive surgery and in a controlled prospective randomized study, the efficacy of: (1) Superfractionated radiotherapy and BCNU; (2) radiotherapy and the radiosensitizer Misonidazole followed by BCNU; (3) radiotherapy and Streptozotocin; (4) BCNU and radiotherapy.

At the present time, 86 patients have been randomized to this study by the University of Tennessee. There have been 34 deaths from tumor progression and four deaths from secondary medical problems.

Seven Veterans Administration patients have been randomized to the study and five are still receiving treatment.

This protocol is anticipated to complete patient accrual by October 1, 1980.

We are observing a longer survival in the patients being treated on the study. Through experience, we have been able to more effectively control the immediate toxicity to the chemotherapeutic agents by the use of specific antiemetic drugs. We are observing a greater amount of myelosuppression in the hematologic monitoring of patients treated than we have experienced in the past. There have been no major complications because of myelosuppression.

367. RANDOMIZED PHASE III PROTOCOL FOR EVALUATION OF MISONIDAZOL COMBINED WITH RADIATION IN TREATMENT OF PATIENTS WITH BRAIN METASTASIS

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The work on this project has actually started and one patient has been included as per our previous memorandum. The initial report for this protocol is the subject of this memorandum.

This protocol compares two fractionations of radiation therapy to patients presenting with brain metastasis from different primaries, excluding lymphomas. It compares two regimens of radiation: (1). Three thousand rads to the brain in two weeks at daily increments of 300 rads for 10 increments. (2). Fractionation of 500 rads twice weekly for 6 increments (total of 3,000 rads in 3 weeks in 6 increments). These two fractionations are compared with and without Misonidazol, a drug which has been found to be a radiosensitizer.

Patients are randomized by the Central Office of Radiation Therapy-Oncology Group, and are assigned to one of the four arms of the treatment. So far, only one patient has been entered into this study.

368. PROTOCOL OF TREATMENT FOR NEUROBLASTOMAS USING SURGERY, RADIOTHERAPY, CHEMOTHERAPY - PHASE III

Lobo, J. F., Garcia, L., Vargas, G., Camacho, M. A., Carrillo, H. J., Jimenez, B. R., Jimenez, E., Navarrete, M., Mora, L., Hospital Nacional de Ninos, Depto. de Onco-Hematologia, *Apdo. 1654, San Jose, Costa Rica*

OBJECTIVE: To improve survival through therapeutic approach in relation to age and extent of disease.

APPROACH: Under 1 year: Stages I and II: resection and chemotherapy; Stages III and IV: chemotherapy (vincristine, cyclophosphamide, adriamycin). Over 1 year: Stages I and II: resection, chemotherapy, radiotherapy. Stage III: chemotherapy, radiotherapy with 60Co. Stage IV: chemotherapy. Controlled trial.

PROGRESS: Twenty-five cases under study. (Translated)

369. SOUTHWEST ONCOLOGY GROUP PROTOCOL 7811, BRAIN METASTASES PROTOCOL, PHASE III

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

This protocol is designed to determine the effectiveness of combined radiotherapy and metronidazole (Flagyl) in the treatment of patients with brain metastases from primary malignancies outside the central nervous system compared with radiation therapy alone. Flagyl is a known radiation sensitizer. The end point will be objective response (brain and/or cat scan improvement) and/or increase in functional neurological level and duration of response. The study will also be designed to test the toxicity of multiple dose administration of metronidazole and radiation therapy. Patient must have histological proof of primary malignancy. There must be clinical suspicion of brain metastases documented by isotope brain scan and/or cat scan and/or neurologic status level of 2 to 4. Patients will not receive concomitant chemotherapy with agent known to pass the blood brain barrier per metronidazole in combination with the whole brain. Radiation has been used in patients with primary brain tumors and shown to have an enhancement of survival. This study is designed to determine that effect in patients with brain tumors metastatic from sites outside the central nervous system.

No patients have been entered on this study to date.

370. PROTOCOL OF TREATMENT FOR RETINOBLASTOMA USING SURGERY, RADIOTHERAPY AND CHEMOTHERAPY - PHASE III

Lobo, J. F., Guerrero, L. J., Piza, E. J., Camacho, M. A., Hospital Nacional de Ninos, *Apdo. 1654, San Jose, Costa Rica*

OBJECTIVE: To establish the usefulness of treatment comprised of surgery, radiotherapy and chemotherapy according to stage of tumor.

APPROACH: Determination of stage: Stage 1 - surgery; Stage 2 -chemotherapy for 1 year (vincristine plus cyclophosphamide), surgery; Stage 3 - surgery, radiotherapy and chemotherapy using vincristine, cyclophosphamide, methotrexate; Stage 4 - same as 3 plus radiotherapy to metastases. Controlled trial.

PROGRESS: Twenty-five patients under evaluation. (Translated)

371. ADJUVANT THERAPY OF BREAST CARCINOMA - PHASE III - TWO YEAR LOW DOSE VERSUS ONE YEAR HIGH DOSE CHEMOTHERAPY WITH RADIATION THERAPY

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OBJECTIVE: To compare the toxicity and the effect on disease free interval and survival of two chemotherapy regimens as adjuvant treatment following mastectomy for women with breast carcinoma and four or more involved axillary lymph nodes.

APPROACH: Eligiblity requires pathologic confirmation of primary and axillary nodes, resection within 6 weeks of study entry, age 65 or under and informed consent. All patients will receive postoperative radiation to supraclavicular and internal mammary nodes. Stratification factors include menopausal status and estrogen receptor status. Randomization to: ARM I LACT; cyclophosphamide 300 mg IV, methotrexate 25 mg IV, 5-fluorouracil 500 mg IV and vincristine 1 mg IV day 1 each 3 weeks for 2 years, commencing after radiation therapy. ARM II LMF-Pred; chlorambucil 4 mg/M2 po daily days 1-14; methotrexate 40 mg/M2 IV days 1 and 8; 5-flurouracil 600 mg/M2 days 1 and 8. Prednisone 10 mg at midnight days 1-14. Cycles each 28 days for 1 year. Note: 2 cycles will be administered prior to radiation therapy.

PROGRESS: New study; no patients yet entered.

372. PHASE I-II STUDY OF HEMIBODY RADIOTHERAPY IN PATIENTS WITH PROGRESSIVE SMALL CELL BRONCHOGENIC CARCINOMA OF THE LUNG

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THERAPY: Upper hemibody irradiation, 400 rad/wk x 4 (single patient planned for 200 rad/2X/wk x 4). Number of patients entered: 7 (5 in FY 79-80).

RESPONSE DATA: CR-0, PR-0, MR-2, NR-4, NE-1; (lost to F/U).

TOXICITY DATA: Treatment related deaths: none. Non-hematologic toxicity: N and V x 2-12 hours in most patients. Severe hematologic toxicity: No sepsis, 2 required platelet Tx'x. Unexpected hematologic toxicity: only 1/7 patients was able to complete scheduled irradiation due to early onset of hematologic toxcity.

FUTURE PLANS: Plans to give HBI in a lower escalating schedule of 200 (then 300, then 400 in serial patients) rad/wk x 4, in conjunction with radioprotector WR-2721, to evaluate whether scheduled irradiation can be given in this way and hopefully allow sufficient irradiation to be delivered to induce response.

373. PHASE III CLINICAL TRIAL OF CHEMOTHERAPY AND RADIOTHERAPY IN THE TREATMENT OF SMALL-CELL CARCINOMA OF THE LUNG (ABBREV)

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OBJECTIVE: To examine in a multicenter clinical trial whether in patients with small-cell carcinoma of the lung of limited extent, treatment with chemotherapy given both before and after radiotherapy is more effective than chemotherapy starting after the radiotherapy.

APPROACH: Histologic type and clinical stage of cancer - Patients with small-cell carcinoma of the lung confined to the mediastinum, the soft tissues of one hemithorax, and the ipsilateral and contralateral scalene and lower cervical nodes are being studied. Treatment modalities and agents - Patients are being assigned at random either to 2 pulses of chemotherapy followed by radiotherapy, followed by further chemotherapy (C3RtC3), or to radiotherapy followed by chemotherapy (RtC3).

PROTOCOL OUTLINE: The radiotherapy consists of a supervoltage midline dose of 3000 rad in 15 fractions over 3 weeks (or a suitable biological equivalent). The chemotherapy consists of alternating 3-drug and 2-drug pulses at 3-week intervals. The aim is to give a total of 10 pulses, but physicians can give more if patients are responding well. Cyclophosphamide 500 mg/sq.m plus methotrexate 50 mg/sq.m is given by I. V. injection at 3-week intervals for 10 pulses. CCNU 50 mg/sq.m is given orally on the first and alternating pulses thereafter. The C3RtC3 patients receive the first 2 pulses of their chemotherapy before the radiotherapy, and the rest afterwards. The RtC3 patients receive their radiotherapy first and then their chemotherapy. Present status - Intake in progress; completion date estimated to be Autumn 1979.

374. PROTOCOL 34B - POSTOPERATIVE IRRADIATION IN PATIENTS WITH RESECTED NONMALL-CELL CARCINOMA OF THE LUNG WITH LYMPH-NODE METASTASES

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This study has been designed to evaluate the effect of postoperative radiation therapy on survival in patients undergoing a curative resection for non-small cell cell carcinoma of the lung with lymph node metastases. In addition, the disease free interval from resection to recurrence will be analyzed. All male patients undergoing a curative resection (no microscopic evidence of residual disease) for non-small cell carcinoma of the lung with documented lymph node metastases will be eligible for inclusion in this study. The eligible patients will be randomized between the 14th and 28th postoperative day into one of the two treatment groups: 1) A control group treated with an operation alone and 2) a group treated with resection plus 175-200 rads per day, five days per week for a total dose of 5,000 rads. Both groups will be followed in a similar fashion. Long-term survival will demonstrate whether postoperative radiation is more effective. The recent reports of Kirsh and Green have suggested that there is an improved survival in patients with carcinoma of the lung with lymph node metastases treated with postoperative radiation. The five year survival rate was approximately 35 percent in patients treated with postoperative radiation as compared to 3 percent in similar patients undergoing resection alone.

375. RTOG 79-13 - PROTOCOL TO STUDY TWO RT FRACTIONS PER DAY IN TREATMENT OF SQUAMOUS CELL CANCER OF ORAL CAVITY, PHARYNX, LARYNX AND SINUSES

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OBJECTIVES: 1) To determine if local control of primary head and neck cancer can be improved using hyperfractionation over conventional fractionation. 2) To evaluate patient acceptance and tolerance of normal tissue to twice daily fractionated treatment. 3) To determine if inoperable lesions can be made operable by altered fractionated technique of administering radiation therapy. 4) To determine survival rates of each fractionated technique.

RESEARCH PLAN: Patients will be randomized according to site and stage of tumor. Arm A: Conventional RT, 600 rad in 33 fractions to 7380 in 41 fractions at 180-200 rad per fraction, 5 fractions/week. Arm B: Two fractions per day of 120 rad separated by 3-6 hours, 6000 rad, 5 weeks.

Criteria of response (CR, PR, MR, NC, PD) will be made at day 90 to 120; weekly measurements will be made of the status of the neck, during the course of therapy. In addition assessments will be made of the degree of rehabilitation of the patient, swallowing function, and performance status.

STATISTICAL CONSIDERATIONS: 1) For a majority of the patients in both arms, high dose photon therapy will be the only treatment. 2) For the various disease sites the 2-year survival can vary from 10-15% to 40-50%. 3) With 4-5 institutions participating in this study the accession rates should be 50 cases per year from all the disease sites. 4) In order to show a statistically significant 11-15% difference in the local controls, over 100 patients from each site will be required. Therefore, it should take from 2-3 years to complete this investigation.

376. PROTOCOL 28 - VA ADJUNCT STUDY OF CANCER CHEMOTHERAPY - COLON-RECTUM PREOPERATIVE X-RAY TRIAL II

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This is a continuing cooperative study of the effects of preoperative radiation for rectal adenocarcinoma. There are 300 patients in the study and the study to date appears to show benefit from preoperative radiation by reduction of the number of positive lymph nodes in resected specimens as compared to controls.

377. NSABP PROTOCOL R-01 - EVALUATION OF POST-OP RADIATION AND SYSTEMIC CHEMOTHERAPY IN MANAGEMENT OF RESECTABLE RECTAL CARCINOMA (ABBREV)

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For patients receiving treatment, this study will compare the length of the disease-free interval and survival of patients who have had a 'curative' resection of adenocarcinoma situated at or distal to the peritoneal reflection (rectum) with that of patients who are receiving systemic chemotherapy or regional radiation therapy in addition to operation. Patients with Dukes' A and D rectal lesions will be included in the study but only for information relative to pathology of their tumors.

To date, there have been five patients at Audie Murphy Veterans Administration Medical Center who have been entered into the NSABP rectal protocol. Study is still ongoing and patient accrual is continuing. There are no early data available for disclosure at the present time. No particular problems, side effects, or untoward toxicity have been noted in the treatment regimen.

378. ADJUVANT THERAPY OF SURGICALLY OPERABLE RECTAL CARCINOMA, STAGE B2 AND C

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This is a randomized Phase III clinical trial designed to compare the usefulness of adjuvant chemotherapy and/or radiation therapy with a surgery-only control group in patients who have received a curative resection for Dukes' B2-C2 adenocarcinoma of the rectum.

As of 2/79, 197 patients from 13 institutions have been randomized into the study. The University of Miami has randomized 16 of the 197 and 6 of the 16 are VAH patients. The study has been active for 44 months during which time 35/197 recurrences have been reported. Fourteen of the 35 patients who had recurrence of disease have died. One out of 17 patients has died free of disease of causes unrelated to either disease or treatment and 8/17 were unexplained at the time of this update.

It is too early to draw conclusions from this study. This protocol is projected to continue through 5/1/80.

379. PHASE I TRIAL OF CIS-DIAMINEDICHLOROPLATINUM (NSC 119875) (DDP) COMBINED WITH SMALL FIELD PELVIC RADIATION THERAPY (ABBREV)

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The purpose of this Protocol is to assess the toxicity associated with the concurrent administration of DDP with small field pelvic radiation therapy by external beam. Our hypothesis is that this combined regimen will not have a major complication rate of more than 10%.

The plan is also to evaluate, when possible, therapeutic response and to make assessments of tumor and host characteristics as they relate to tumor response and possible patient toxicity, particularly: (1) To evaluate cystoscopically the response rate of the primary bladder tumor in patients with known visible residual disease. (2) To assess the duration of tumor response (disease-free interval), pattern of failure, site(s) of recurrence(s) and patient survival. (3) To assess the following parameters that possibly may influence patient tolerance or therapeutic response: (a) histologic type, grade and stage, as well as configuration (papillary, sessile or flat, based on both gross and microscopic findings) of the primary bladder tumor, (b) the presence of demonstrable invasion of lymphatics and/or blood vessels in the primary tumor (elastic tissue stain) and (c) age and sex.

The plan is to register 25 patients. It is anticipated that this pilot study will not give statistically significant information with regard to the primary bladder tumor response rate (local control rate), nor the incidence of the development of distant metastases. However, this pilot study nevertheless is important for documenting that this rational combined regimen is tolerable and clinically acceptable as an approach to patients with invasive primary bladder carcinoma who are unsuitable for cystectomy.

380. ADJUVANT CHEMOTHERAPY (VCA) AFTER RADIOTHERAPY IN NASOPHARYNGEAL CARCINOMA

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The project aims to verify the effectiveness of an adjuvant long-term polychemotherapy treatment (VCR plus ADM plus CTX) after radical radiotherapy in nasopharyngeal carcinoma. All patients with histologically proven NPC in local-regional phase (except T1N0 and TxNxM1) receive full dose radical teleradiotherapy (60-70 Gy) (60Co, Line Ac., electron beam) including nasopharynx, base of skull, neck lymph nodes in both sides (including supraclavicular nodes). Six weeks after the end of RT patients with complete regression of T and N are randomized between no further treatment and adjuvant chemotherapy (VCR 1.2 mg/m2 i.v. (day 1) plus CTX 200 mg/m2/day (days through 4), per course). A course of CT is given every 4 weeks during 12 months. Patients with complete regression of T and PR and N are treated with radical neck dissection before randomization. Survival and length of disease-free interval will be the criteria for evaluation. The trial is multicentric, with 21 Cooperative Centers in Italy. Protocol and forms are also made for hospital-based registry of NPC in this country. An epidemiological form will be also available in a short time. The trial was activated Dec. 3, 1979. Fifteen cases have been included (Dec. 31, 1979).

381. SWOG-7965, TREATMENT OF EARLY SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK WITH INITIAL SURGERY AND/OR RADIOTHERAPY FOLLOWED BY CHEMOTHERAPY

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

This study is designed to determine if the disease-free interval and survival of patients who have squamous cell carcinoma of the head and neck, and who are at higher risk of relapsing, can be improved by adjuvant methotrexate following initial surgery, radiotherapy or both. The surgery and/or radiotherapy both are designed to create a situation where there is no clinically evident disease. This study will require at least 76 patients, who have relapsed in each of the treatment arms. Based on an annual accrual rate of 200 patients from the group, it would take approximately 28 months to complete.

382. TREATMENT OF NEWLY DIAGNOSED STAGE IV UNRESECTABLE EPIDERMOID CA OF HEAD AND NECK (ABBREV)

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Patients initially presenting with Stage IV unresectable squamous cell carcinoma will be randomized and stratified into three treatment arms. Arm I: cis-platinum (100 mg/m2) on days 1 and 22 plus bleomycin (15U/m2/day) on days 3-9 followed by radiotherapy. Arm II: bleomycin (15U/m2/day) on days 1-7 followed by radiotherapy. Arm III: radiation therapy alone. Seven thousand to 7500 rads will be delivered to the primary and 6000 to 6500 rads to neck metastases. The remainder of the supra-clavicular neck will receive 5000 rads. Five fractions per week of 180 to 200 rads will be employed.

Six weeks after completion of radiotherapy patients will be endoscopically re-evaluated as to future operative ability, complete response or need for further chemotherapy. In selected patients, biopsy and surgical material will be processed for stem cell assay and used to compare in vitro the patient response to the treatment agents.

Patients will be considered off protocol under the following conditions: drug toxicity, failure of tumor to respond to therapy, patient choice or marked decline in performance status. Finally, in order to protect the patient, any treatment arm may be discontinued if there arises a statistically significant poor response to that form of therapy.

383. A PROTOCOL FOR THE TREATMENT OF ADVANCED INOPERABLE CARCINOMA OF THE HEAD AND NECK

Spaulding, M., Lore, J., Sanani, S., Dayem, H., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Medical Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

Two patients have been treated with a protocol entitled Treatment of Advanced Unresectable Carcinoma of the Head and Neck. This project is designed to investigate the use of simultaneous chemotherapy with irradiation in patients who have advanced unresectable tumors. The two patients have tolerated the treatment well although there has been severe mucositis. The mucositis was expected and was tolerated by the patients. It is too early to tell whether the hypothesis, i.e. that control of unresectable disease will be improved by the simultaneous administration of chemotherapy and radiation, will be proven.

384. MISONIDAZOLE ADJUVANT TO RADIOTHERAPY IN HN CANCERS

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This project has been approved by NCI under the usual RTOG mechanisms and has been active since 10/79. Approximately 80 patients have been entered into this phase III trial testing 'standard' X-ray therapy in T3/T4 squamous cancers of the HN area versus 'standard' X-ray therapy (slightly modified) and 2.0 gm/mm2 of Misonidazole once weekly for 6 weeks. The endpoints are local control/survival.

385. RADIOTHERAPUTIC CONTROL-MULTIPLE SESSIONS IN A DAY FRACTIONATION

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Since January 1978 we have done the following 1) the literature has been reviewed, 2) the protocol has been written, 3) before the official beginning of the controlled study, we treated some patients according to the protocol. In the future these patients will be include if possible in the study.

By August 31, 1979 we treated 30 patients (17 with oral cavity tumors, 5 with oropharyngeal tumors, 8 with maxillary antrum tumors). After the official starting of the protocol, that is between September 1, 1979 and December 31, 1979 we treated 15 patients (4 oral cavity tumors, 11 oropharyngeal tumors). We evaluated the cases treated with multiple sessions in a day regimen collected from 1975 to June 1978 and we compared them with similar cases treated with conventional fractionation.

Encouraging results of this study have been presented at XIII Congresso, Nazionale di Radiobiologia, Florence, October 12-13 and we plan to continue our studies to increase our experience collecting a larger number of patients. For this reason the study will continue until August 31, 1982.

386. SEG PROTOCOL STUDIES

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These are 30 clinical protocols for studies of new combinations of drugs and/or radiation therapy for the treatment of malignant diseases. They are designed by the Southeastern Cancer Study Group, approved by the National Cancer Institute and by the Food and Drug Administration. The protocols are studies for a series of tumor types with defined methods of administration of drugs and monitoring of disease activity for each group of cancers. Cooperative studies permit standardization of therapy within a group of institutions so that better statistical evaluation of the efficiency of treatment can be carried out. Generally we would expect to enter approximately 40 patients per year on these protocol studies. Results from each institution are summarized using a statistical office at the University of Alabama Medical Center. The aim of the project is to develop better methods for the treatment of cancer.

C. RADIATION THERAPY COOPERATIVE GROUPS

387. RADIATION THERAPY ONCOLOGY GROUP

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This project provides support for the participation of the Radiation Oncology Division of the University of Puerto Rico in the Radiation Therapy Oncology Group. This organization consists of a national group of academic institutions involved in prospective clinical research in radiation therapy of cancer.

The University of Puerto Rico began its participation in the Radiation Therapy Oncology Group early in 1972. Study cases are contributed by the University Hospital, the San Juan City Hospital, and the Radiotherapy Institute of the Metropolitan Hospital, all of which form part of academic radiation therapy program. An additional institution, the San Juan Oncologic Hospital, may begin accessing case.. during FY 1981.

This program contributes: case registration in RTOG registries, case accession for groupwide protocols, pilot Phase II study cases, protocol development, committee participation, and scienific publications.

388. RADIATION THERAPY ONCOLOGY GROUP

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The Radiation Therapy Oncology Group is a group of radiation therapy research and clinical centers which conduct highly disciplined joint clinical investigations.

The group has the following objectives: a. To undertake clinical trials and other cooperative studies in an endeavor to advance knowledge of radiation therapy while improving the curative and palliative management of cancer. b. To improve the control of primary and regional disease. c. To reduce treatment morbidity and complications from radiation therapy, while maintaining control of primary and regional disease. d. To collaborate with other oncology disciplines to obtain data on optimal multimodality therapy, particularly in areas where radiation therapy plays a major role.

The group is ably supported by an operational headquarters which assists the Chairman and Executive Officer in the management of the group with particular emphasis placed on its quality control program.

A sophisticated biostatistical center exists as part of the Radiation Therapy Oncology Group and is ensuring statisfactory methodology of its studies. The center also aids in establishing an order of priorities for these important studies.

389. RADIATION THERAPY ONCOLOGY GROUP

Marks, R. D., Fitzgerald, R. H., Moore, T. N., Wallace, K. M., Adkins, W. Y., Medical University of South Carolina, School of Medicine, Dept. of Radiation Therapy, *80 Barre St., Charleston, South Carolina*, 29401, United States of America

Support is requested in this application for expanding the participation of the Division of Radiation Oncology of the Medical University of South Carolina in the activities of the Radiation Therapy Oncology Group. This department participates in radiation oncology programs at the Medical University of South Carolina and affiliated Roper Hospital in Charleston. The Division treats approximately 1200 patients a year, 1000 of these being new cancer patients. The Radiation Oncology Divi-

sion has participated in the Radiation Therapy Oncology Group since 1973 and has been an active member since January 1974. Subsequent to the data above, approximately 200 cases have been accessioned into the various protocols of the Radiation Therapy Oncology Group. The Principal Investigator has been active in attending all meetings since 1974 and recently was appointed a member of the Site Visit Committee and a member of the Nominating Committee for the Group. The Principal Investigator has been an active participant in all working parties and has recently authored a Pilot Study involving hyperfractionation. To date the Division has entered a number of patients in the Lung Protocol, a split course protocol, mainly involving patients with carcinoma of the cervix, and the Head and Neck Protocol. At the present time we have submitted a contract proposal for the proposed study involving chemotherapy, radiotherapy, and surgery in treatment of advanced carcinoma of the head anc neck.

390. RADIATION THERAPY ONCOLOGY GROUP

Mann, S. G., Sklaroff, D. M., Asbell, S. O., Schlager, B., Baker, A., Johnston, S., Reig, N., Albert Einstein Medical Center, Dept. of Radiology, *York & Tabor Rds., Philadelphia, Pennsylvania,* 19141, United States of America

The objective of this proposal is the support of co-operative clinical trials under the supervision of the Radiation Therapy Oncology Group of the National Cancer Institute (RTOG) and in cooperation with other national cooperative clinical research groups, e.g. GOG, (Gynecological Oncology Group), etc. Personnel and facilities will be utilized for extensive staging workup as well as radiation therapy treatment planning and administration according to the standards of these cooperative groups. Improvements in the results of palliative and curative radiation therapy are expected from this research.

391. RADIATION THERAPY ONCOLOGY GROUP

Brady, L. W., Hahnemann Medical College & Hospital, Medical College, Dept. of Radiation Therapy & Nuclear Medicine, *235 N. 15th St., Philadelphia, Pennsylvania,* 19102, United States of America

This institution is a participant in the Radiation Therapy Oncology Group. Overall goals of the Group and the Study Protocols are described in the Group Chairman's renewal application. Our institution will continue to register all new protocol cancer patients with the Group Operations office and shall continue to participate in the Group Studies listed in a later section of this application. New protocols will be added as they become available. Moreover, our institution will coordinate and encourage the efforts of selected affiliated hospitals which are being enrolled in the program of national clinical cooperative trials.

392. RADIATION THERAPY ONCOLOGY GROUP

Mohuiddin, M., Thomas Jefferson University, Jefferson Medical College, Dept. of Radiation Therapy & Nuclear Medicine, *1025 Walnut St., Philadelphia, Pennsylvania,* 19107, United States of America

This application is to permit the joining with other institutions through the centralized Headquarters Office of the Radiation Therapy Oncology Group, for the purpose of adding patients to randomized protocols for joint clinical trials to determine the best course of treatment through statistical analysis. Improvement in results from both palliative and curative radiation therapy is the goal of this research. The coordination of efforts of affiliated institutions will broaden the scope of the program.

The group also participates in non-randomized studies such as pilot studies, phase II studies, and registries.

The professional staff of the Department also participates in the work of the RTOG Headquarters Office, which is located in close proximity to Thomas Jefferson University Hospital.

393. RADIATION THERAPY ONCOLOGY GROUP

Goodman, R. L., Littman, P., Glick, J., Bloch, P. H., Carabell, S. C., University of Pennsylvania, School of Medicine, Dept. of Radiation Therapy, *36th & Hamilton Walk, Philadelphia, Pennsylvania,* 19174, United States of America

The University of Pennsylvania (UP) is a member of the Radiation Therapy Oncology Group (RTOG). It not only contributes large numbers of patients, especially those with head and neck tumors, but both radiation therapy and non-radiation therapy specialists contribute time and effort in committee work and in providing consultative services. Thus, the University of Pennsylvania exemplifies in its activities a commitment to the interdisciplinary approach to patients with oncological diseases and assists RTOG, a cooperative group of radiation therapy research and clinical centers, in the conduct of joint clinical investigations. The group conducts randomized clinical trials and other cooperative clinical studies to advance knowledge in the cure and control of cancer by gathering adequate numbers of patients necessary for the answer to important clinical questions. It also makes possible the collection of long-term data with regard to radiation complications and patient survival, and promotes multi-disciplinary care by integrating its study programs with those of other disciplines. In that way, it also enriches training programs in oncology as well as radiation therapy.

394. CANCER CONTROL PROGRAM - RADIATION THERAPY GROUP

Kramer, S., American College of Radiology, *925 Chestnut St., Philadelphia, Pennsylvania,* 19107, United States of America

OBJECTIVE: Establish and promote cancer control programs for clinical cooperative groups. This is for such programs within the Radiation Therapy Oncology Group (RTOG).

395. RADIATION THERAPY ONCOLOGY GROUP

Concannon, J. P., Allegheny-Singer Research Corp., *320 E. North Ave., Pittsburgh, Pennsylvania,* 15212, United States of America

Funding is requested to continue the participation of Allegheny General Hospital in the clinical trials of the Radiation Therapy Oncology Groups.

396. RADIATION THERAPY ONCOLOGY GROUP

Chang, C. H., Tretter, P. K., Harisiadis, L., Sung, D. I., Oster, M., Housepian, E. M., Abramson, M., Rankow, R., Wolff, J., Perzin, K., Kessaris, N., Columbia University, College of Physicians & Surgeons, Dept. of Radiology, *630 W. 168th St., New York, New York,* 10032, United States of America

This research proposal is to continue participation on a cooperative group of Radiation Therapy Centers in the United States (known as Radiation Therapy Oncology Group) for the purpose of conducting joint clinical investigation in an endeavor to advance knowledge in the curative and palliative management of cancer.

This institution has participated in several protocols in clinical trial: Phase I/II protocol for evaluation of Misonidazole Combined with Radiation in the Treatment of Patients with Malignant Glioma. Phase I/II Study of Hyperthermia Treatment Technique and Tolerance of Skin and Subcutaneous Tissues to a Temperature of 40-45 degrees C, and other protocols which were reported previously.

Several Phase III protocols evaluating hypoxic cell radiation sensitizer have just been activated and we are participating in these studies. These include: Phase III Protocol for Malignant Glioma -Standard Radiotherapy Plus BCNU Chemotherapy Compared to Radiosensitized Radiotherapy Plus BCNU Chemotherapy; Phase III Study to Compare Misonidazole Combined with Irradiation or Radiation Therapy Alone in the Treatment of Locally Advanced (Stage III) Non-Oat Cell Lung Cancer.

397. RADIATION THERAPY ONCOLOGY GROUP

Abitol, A., New York Medical College, Manhattan Campus, School of Medicine, Dept. of Radiology, *1249 5th Ave., New York, New York,* 10029, United States of America

This institution is a full member of the Radiation Therapy Oncology Group (RTOG); the group is composed of collaborating institutions formed to evaluate cancer treatment protocols in prospective controlled randomized clinical trials. Overall goals of the Group and the study protocols are described in the Group Chairman's renewal application. Cooperative studies are undertaken to advance knowledge in the curative and palliative management of cancer. Conducting such investigations within individual institutions is restrictive because of limited patient material. The pooling of patient material by member institutions overcomes this limitation.

Treatment protocols subjected to study involve various cancers and their multi-disciplinary management by radiothera-

py, surgery and chemotherapy. The protocols are under the strict supervision of the Radiologic Physics Center with data analysis conducted by the Biostatistical Center of the Group. Long-term data will be collected with regard to patient survival, quality of survival and complications of treatment. New protocols will be added for Group Study as they become available.

398. RADIATION THERAPY ONCOLOGY GROUP

Newall, J., Carella, R., Cooper, J. S., Barish, R. J., Lerch, I. A., Farina, A., Gorstein, F., New York University, School of Medicine, Dept. of Radiology, *100 Washington Sq. E., New York, New York*, 10003, United States of America

In recent years the importance of critical analysis of the efficacy of various methods of cancer treatment has received much emphasis. The necessity of comparing like situations has led to the development of controlled clinical trials. Because of the necessity to have large numbers of patients for proper statistical comparison and the difficulty of realizing these numbers within individual centers, it has become necessary to form groups in which various centers pool material. The Radiation Therapy Oncology Group was formed to assess the efficacy of radiation therapy in the treatment of various malignancies using various techniques alone or in combination with other forms of cancer treatment, as well as the investigation of innovative measures involving altered time-dose shedules and the combination of Radiotherapy with sensitizers, protectors and hyperthermia.

Treatment protocols are under constant professional analysis by the physician of the group with supervision and help from the Biostatistical Center. The quality of radiation therapy is monitored by the Radiologic Physics Center. In addition to the analysis of treatment methods and results, information obtained includes long-term review of the complications of radiation and the establishment of an information center for analyzing results of radiation in rare tumors and using unusual techniques. New York University Medical Center has been a full member of the group since 1973.

399. RADIATION THERAPY ONCOLOGY GROUP

Rubin, P., University of Rochester, School of Medicine & Dentistry, Dept. of Radiation Oncology, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

The RTOG is a cooperative group of radiation therapy research and clinical centers organized for the purpose of conducting joint clinical investigations. The Division of Radiation Oncology of the University of Rochester Cancer Center is one of the member institutions of the RTOG and the Office of Protocol Design and of the Vice-Chairman are located within it. A listing of the major RTOG objectives and progress that has been made by the group, both nationally and at this institution, is described and includes: case accession, new research areas, standardized treatment planning, quality control, neutron clinical investigation, study registries and forms, and the interaction of the RTOG with other cooperative groups. The protocol design activities of the RTOG are reviewed through two schemes: First, major radiation themes which can apply to many disease sites: time dose factors, radiosensitizers, systemic irradiation, high LET irradiation, optimal time of radiation therapy and chemotherapy, hyperthermia, combining innovations in radiation therapy and mathemtical modeling; second, disease sites in terms of unique specific studies, especially studies of brain, lung, head and neck, genitourinary and metastatic disease. The activities of the Division of Radiation Oncology in protocol accession and the studies which are chaired by members of this institution are reviewed.

400. RADIATION THERAPY ONCOLOGY GROUP

Johnson, R. J., Friedman, M., Panahon, A., Chen, T. Y., Krishnamsetty, R. M., Pearce, J., Suhjack, J., Dannels, J., Henderson, R., Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York*, 14263, United States of America

This grant allows participation in the RTOG cooperative trials for Phase I, II and III studies. Participation in Phase I and II studies has been involved with radiation sensitizers and hyperthermia.

The hyperthermia studies have required development of microwave generators, applicators and methods of thermal measurement. Roswell Park Memorial Institute has been one of the leading research institutes in the development of microwave applicators.

Clinical participation in Phase III protocols will be concentrated on curable rather than metastatic protocols.

The development work in hyperthermia both in the past and at present is supported by RTOG funds only.

401. RADIATION THERAPY ONCOLOGY GROUP

Hendrickson, F. R., Rush University, School of Medicine, Dept. of Therapeutic Radiology, *1725 W. Harrison St., Chicago, Illinois*, 60612, United States of America

This application is to support continued participation in the Radiation Therapy Oncology Group research protocols. The primary objectives are to improve the effectiveness, efficiency, logistics and economics of cancer management by radiation therapy alone, and in combination with surgery and/or chemotherapy. The primary commitment is to achieve these ends through the cooperative group mechanism, recognizing that few institutions have sufficient breadth and depth of material and personnel to answer such questions in a reasonable time frame. New areas for investigation may be developed in a pilot study mechanism for ultimate development into group-wide protocols. The ultimate culmination of this process will be the transfer of current research information to implementation at the community level. Rush has been actively involved in developing cancer control outreach activities for four of our major affiliated institutions.

402. RADIATION THERAPY ONCOLOGY GROUP

Perez, C. A., Washington University, School of Medicine, Dept. of Radiology, *660 S. Euclid Ave., St. Louis, Missouri*, 63110, United States of America

The Division of Radiation Oncology at Washington University proposes to: 1) Continue participation in clinical trials of the Radiation Therapy Oncology Group; 2) contribute to the scientific contents of group studies and to actively engage in protocol design and coordination; 3) assist in administrative and organizational matters of the group outlined by the Chairman of the Group and Committee Chairmen; 4) participate in the analysis of scientific data generated by the Radiation Therapy Oncology Group and to prepare manuscripts to be submitted for publication to reputable scientific journals; 5) promote clinical trials within the framework of cooperative groups at Washington University School of Medicine. The Division has consistently been one of the major contributors of patients to RTOG protocol studies. Approximately 50% of the patients accessioned to the studies have been in non-metastatic protocols. The projected number of patients to be entered in protocol studies during the year 1979 will be in the range of 90 to 100. The Division participates in the avant-garde protocols in radiation oncology that require specialized facilities and equipment such as the hyperthermia and hypoxic sensitizers.

403. RADIATION THERAPY ONCOLOGY GROUP

Doss, L. L., Cancer Research Center, Dept. of Radiation Therapy, *Garth Ave. & Hwy. 40, P.O. Box 1268, Columbia, Missouri*, 65201, United States of America

The radiation Therapy Oncology Group (RTOG) was organized in 1971 as a group of research and clinical centers dedicated to conducting clinical trials on the premise that a cooperative approach to the design and conduct of such trials would be of significant benefit to a large patient population. The RTOG is dedicated to the goal of improving the care of patients with malignant disease and increasing their survival rate through research and multidisciplinary study.

The RTOG's objectives are: To constitute a group of clinical radiation therapy investigative centers dedicated to cooperative clinical trials; to define clinical priorities for radiation therapy studies and establish standardized treatment parameters; and to define radiation and ancillary equipment needs for clinical trials. The RTOG develops strategies for treatment of all types of tumors and stages for various sites.

404. RADIATION THERAPY ONCOLOGY GROUP

Fu, K. K., Phillips, T. L., Luk, K., Hill, D., University of California, San Francisco Campus, School of Medicine, Dept. of Radiation Oncology, *551 Parnassus Ave., San Francisco, California*, 94122, United States of America

Support requested in this application is for the ongoing and expanding participation of the Department of Radiation Oncology of the University of California in San Francisco in the activities of the Radiation Therapy Oncology Group. Comprised of three hospitals, Moffitt, Mt. Zion and Franklin, the Department is staffed by eleven full-time faculty members, treating 2000 new patients per year. The Department has participated in the Group since 1972, entering approximately 150 patients into the various Group protocols, pilot studies and registry protocols during the last year. The Principal Investigator is a member of the Head and Neck Committee, Combination Radiotherapy and Chemotherapy Sub-Committee and Hematopoietic Sub-Committee of the Radiation Therapy Oncology Group. The Associate Principal Investigator is Chairman or the Radiobiology Committee and a member of the Publication Committee, Experimental Design Committee, Lung Sub-Committee, Metastases Sub-Committee, Radiation Injury Sub-Committee, Hyperthermia Sub-Committee and Chairman of the Radiosensitizer/Protector Committee and all staff members serve on the working parties. The group has produced protocols for head and neck cancer, non-Hodgkin's lymphoma, brain metastasis, and hypoxic cell sensitizers, as well as providing input into other protocols. Support through this application will allow RTOG participation by the entire Department and its affiliated institution, the University of California, San Diego, Division of Radiation Oncology and increase the case accession rate to 175-200 new patients per year into the various RTOG protocols. Extensive continuing research into chemical and thermic modification of radiation effects and high LET radiotherapy is expected to lead to innovative protocols and correspondingly to increased accession of patients into studies sponsored by the RTOG.

405. RADIATION THERAPY ONCOLOGY GROUP

George, F. W., University of Southern California, School of Medicine, Dept. of Radiology, *2025 Zonal Ave., Los Angeles, California*, 90033, United States of America

The Radiation Medicine Unit of the University of Southern California School of Medicine, through its facilities at the Los Angeles County USC Medical Center and affiliated institutions, intends to continue to expand its participation in individual institutional and joint clinical studies sponsored by the Radiation Therapy Oncology Group.

In the period of the previous project, Grant Number 1R01 CA 18259-03, USC entered 1221 patients onto RTOG studies, and for the most recent yearly reporting period available, calendar year 1977, ranked high in accession to RTOG studies, eight out of thirty-six, and first or second in three of the most active studies, Breast Stage I and II, Bone Metastases, and Brain Metastases. Work in the latter area resulted in a publication by Frank Hendrickson, M.D., 'The Optimum Schedule for Palliative Radiotherapy for Metastatic Brain Cancer.' Records of case accrual for the first 10 months of 1978 indicate an increased rate above 1977. USC faculty authored the active RTOG protocol, Irradiation of Adeno-Carcinoma of the Prostate, Stage B with Positive Pelvic Nodes, 75-06.

During this same period, the research team of the USC Radiation Medicine Unit activated studies evaluating the immune status of radiation therapy patients. In the period of the current application this experience will be expanded to study active immunomodulation in RTOG 78-11 Levamisole and Radiation Therapy in Lung Cancer. During the same period, USC will expand its studies of radiosensitizers, through continued accession to RTOG misonidazole studies, and of hyperthermia both externally and interstitially in combination with irradiation. A network of affiliating institutions has been formed to markedly increase patient accession and to enhance the impact of the RTOG program on the community cancer patient.

406. RADIATION THERAPY ONCOLOGY GROUP

Griffin, T. W., Groudine, M., Kurtz, J., Laramore, G., Russell, A., Tong, D., Wootton, P., University of Washington, School of Medicine, Dept. of Radiation Oncology, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington*, 98195, United States of America

The overall objective of this program is to continue the role of the Department of Radiation Oncology at the University of Washington as a partner in the national complex of radiotherapy research centers (Radiation Therapy Oncology Group) cooperating in clinical trials and allied studies seeking to determine the best treatment methods for patients with cancer.

The University of Washington has participated effectively in accruing patients for randomized studies since 1971. We are currently participating in 13 ongoing studies and 3 registries. Ninety-nine patients have been entered on the studies and 54 on the registries.

407. SOUTHWEST ONCOLOGY GROUP PROTOCOL 7808, COMBINATION MODALITY TREATMENT FOR STAGE III AND IV HODGKIN'S DISEASE MOPP NO. 6

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

This study is designed to attempt to increase the complete remission rate induced with MOP-FAP alone utilizing involved field radiotherapy in patients with Stage III and IV Hodgkin's disease achieving a PR at the end of 6 cycles of MOP-BAP. Also, to determine if immunotherapy maintenance with levamisole or consolidation with low dose involved field radiotherapy will produce significantly longer remission durations over a no further treatment group when CR has been induced with 6 cycles of MOP-BAP in Stages III and IV Hodgkin's disease.

There is a total of 4 patients entered into this study by this institution, 3 of these patients are VA patients and thus far a total of 67 patients have been entered into the groupwide study and it is still ongoing.

408. SOUTHWEST ONCOLOGY GROUP

Dyment, P. G., Doering, E. J., Rothner, A. D., Cruse, R., Erenberg, G., Hahn, J. F., Kay, R., Steiger, E., Price, R., Gidwani, G., Marks, K., Deodhar, S. D., Cleveland Clinic Hospital, Section on Pediatric Hematology/Oncology, *9500 Euclid Ave., Cleveland, Ohio*, 44106, United States of America

This proposal involves a multi-disciplinary/multi-professional research approach to childhood malignancies. This proposal is supported by a clinical research and laboratory research team in a university affiliated pediatric medical center which is actively involved with the Pediatric Division of the Southwest Oncology Group (SWOG). Special emphasis is given to the combination of chemotherapy with other modalities of therapy such as radiation therapy and surgery. The Pediatric Oncology team consists of 2 pediatric hematologist-oncologists, 2 hematopathologists, a pediatric pathologist, a pediatric ophthalmologist, 3 child neurologists, a pediatric thoracic surgeon, an oncologic orthopedic surgeon, a pediatric gynecologist, 2 oncologic gynecologists, 2 social workers, a pediatric oncology nurse, 2 data technicians, a child psychiatrist and a tumor immunobiology support group of 5. All patients under 20 years of age who are admitted to the Cleveland Clinic Hospital are offered the opportunity to take part in SWOG protocols if one is open for their particular disease status. Members of the team are not only actively involved in patient care related to protocol research, but are heavily involved in both protocol design and committee work for SWOG.

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409. DDP WITH SMALL-FIELD PELVIC RADIATION THERAPY FOR PATIENTS WITH LOCALIZED INVASIVE BLADDER CANCER WHO ARE UNSUITABLE FOR CYSTECTOMY

Soloway, M. S., Cox, C., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee*, 38104, United States of America

Protocol 8 of the National Bladder Cancer Collaborative Group A is designed to evaluate the efficacy and toxicity of DDP combined with concurrent administration of small-field pelvic radiation therapy by external beam in patients with clinically localized invasive primary bladder carcinoma who are unsuitable for cystectomy. Patients receive 8 courses of DDP, 70 mg/M2 every three weeks, and 6480 rads given over 7-10

weeks. Patients are evaluated by cystoscopy every 12 weeks, and are followed for five years or until death.

410. CANCER AND LEUKEMIA GROUP B RADIOTHERAPY COMMITTEE

Glicksman, A. S., Reinstein, L. E., Tefft, M., McShan, D., Rhode Island Hospital, *593 Eddy St., Providence, Rhode Island,* 02903, United States of America

This is a request for supplemental funding so that the Radiotherapy Office of the CALGB through its Quality Assurance Program can undertake the quality assurance of two Pediatric Intergroup Studies, the Intergroup Rhabdomyosarcoma Study-2 and the National Wilms' Tumor Study-3. Dr. Melvin Tefft is the radiotherapy representative of the CALGB to both of these studies and is a member of the CALGB Quality Assurance Overseers Committee. The intent at this time is to utilize the organization, procedures, and overall facilities of the CALGB Quality Assurance Program for the two Intergroup Pediatric Studies rather than to establish free-standing, independent, quality assurance programs for IRS-2 and NWTS-3.

411. COMMITTEE FOR RADIATION ONCOLOGY STUDIES

Powers, W. E., Brady, L., Brown, G. S., Cox, J., Hall, E., Hellman, S., Hussey, D., Levitt, S., Perez, C., Rubin, P., Stewart, J. R., Sult, H., Michigan Cancer Foundation, *110 E. Warren St., Detroit, Michigan,* 48201, United States of America

This continuation application seeks continued support for the Committee for Radiation Oncology Studies (CROS) which is a group of 15 leading scientists working together to improve oncology sciences, including those related to radiation therapy, radiation biology, radiation therapy physics, and those scientists concerned with oncology imaging. This Committee will continue to serve as an advisory body to the National Cancer Institute, responding to specific assignments from the director of the NCI and the directors of the divisions of the NCI. The group will serve as an advisory group to the Bureau of Radiological Health and other agencies concerned with radiation sciences concerned with oncology and the care of patients. In addition to reponding to questions posed by NCI staff, CROS will attempt to anticipate and advise on significant matters that relate to radiation oncology and present a statement of the problem or questions and recommendations for solutions.

CROS will also continue to initiate and, in conjunction with other groups, plan and operate multi-disciplinary workshops and 'state-of-the-art' meetings on appropriate topics. The Committee functions as a fully independent body whose sole purpose is to improve the quality of radiation therapy practice and research and the quality of cancer care throughout the country. The Committee is available as a resource for updating the National Cancer Plan and other projects assigned by the National Cancer Institute or other organizations of government.

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